Entered as second class matter May 1 1922, at the post office at Baltimore Maryland, under the act of March 3, 1879

A REVIEW OF EXPERIMENTAL STUDIES OF NON-SPECIFIC INHIBITION OF ANAPHYLACTIC SHOCK

JUSTINA H HILL AND LAY MARTIN

From the Departments of Urology and of Medicine of the Johns Hopkins Medical School and Hospital

This review is limited to studies of non-specific inhibition of the anaphylactic shock which is obtained by the second injection of an antigen Similar studies of the inhibition of anaphylatoxin, peptone and other shocks, of which there is a small but interesting bibliography, have been omitted

The discussion of so extensive a subject as this, one which contains so many conflicting findings or statements of findings, must necessarily be broad Detailed information will be found in the addenda, where the agents have been listed alphabetically, in order to facilitate orientation There, under each agent, an effort has been made to review every publication critically and, where several articles have been published on the use of one agent, a brief summary has been made We believe that the addenda will be of interest mainly to readers who wish to use it in reference to particular substances An idea of the types of agents used for non-specific inhibition of anaphylactic shock, however, may be obtained from the following list, which includes all that we have been able to find in available literature

ALPHABETICAL LIST OF THE AGENTS WHICH HAVE BEEN USED TO INHIBIT ANAPHYLACTIC SHOCK

Acetone
Adrenalectomy
Adrenalin
Agar
Ageing of antigen
Albumoses
Alcohol
Allocaine
Almond oil
Ammonium sulphate
Anaphylatoxin
Animal charcoal
Antitrypsin
"Arsenobenzene"
Atropine
Barium chloride
Barium sulphate
Barometric pressure reduction
Bayer "205"
Bayer "1910"
Benzoic acid
Benzol
Bile
Blood volume increase
Brain surgery
Butyric acid
Caffein
Calcium acetate
Calcium chloride

Calcium lactate
Calcium sulphate
Cascosan
Castration
Chloral hydrate
Chloralose
Chloroform
Cholesterin
Cholin hydrochloride
Complement fixation
Congo red
Curarin
Dextrin
Dialysis of antigen
Diastase
Dichlorathylsulphid
Drying of antigen
Egg fat
Emulsin
Eserine
Ether
Ethyl chloride
Filtration
Formaldehyde
Freezing antigen
Gastric juice
Gelatin
Gland extracts, sexual
Glucose
Glycogen
Guanidine chloride
Heating antigen
Heparin
Hirudin
Hydrochloric acid
Hydrogen peroxide
Ink
Intercurrent infection
Invertin
Iodbenzoic acid
Iodine
Iron, state of hydrosol
Iron oxide
Iron oxide, saccharated
Kephalin
Lanolin
Lecithin
Lipoids, not listed elsewhere
Magnesium sulphate
Manganese chloride
Mercurochrome-220
Mineral waters
Milk
Morphine
Mud
Multiple sensitization
Myrosin
Neoarsphenamine
Nephrectomy
"Novoprotein"
Olive oil
Opium
Orange juice
Oxygen
Pancreatin
Paraldehyde
Pepsine
Peptone
Pilocarpine hydrochloride
Pituitrin
Potassium chlorate
Potassium oxalate
Potassium permanganate
Pregnancy
Pressure
Quinine
Rice, polished
Roentgen ray
Saponin
Seed extracts
Serum fractions
Serum globulin
Serum, heterologous
Serum, normal
Sodium bicarbonate
Sodium carbonate
Sodium chloride
Sodium citrate
Sodium cyanide
Sodium formaldehyde sulphoxylate
Sodium glycholate
Sodium hydroxide
Sodium hyposulphite
Sodium iodoxybenzoate
Sodium nitrite
Sodium oleate
Sodium persulphate
Sodium sulphate
Sodium taurocholate
Splenectomy
Starvation
Stovain
Strychnine
Succinic acid peroxide
Sulphur, colloidal
Sulphur, protein combination
Surgical interference
Tallhamine
Temperature reduction
Thorium X
Thymectomy
Thyroidectomy
Thyroid extract
Toxins
Transfusion
Trikresol
Trypan blue
Ultra violet light
Urethane
Urine
Vagus section
Vitamin A deficiency
Vitamin B deficiency
Vitamin C
Water
Whey protein

Before discussing the types of experimentation employed, certain points in regard to methods of study should be emphasized Owing to the individual variations of the experimental animals, it is absolutely

necessary to use a sufficiently large number of both control and treated animals to allow a determination of the extremes of such variations Closely related to this is the necessity of knowing, granted that a given agent inhibits shock, that the second injection of antigen has been sufficiently large, or, granted that a given agent fails to inhibit shock, that the second injection of antigen has not been excessive This would seem quite obvious, and would not have been mentioned, had we not been forced to read article after article in which one or two controls and treated animals were offered as conclusive evidence, or in which no titration of antigen was given

Since it is desirable not to employ an antigen dosage increased to the point of killing the least sensitive animal, which would be much more than a lethal dose for the average, one may not expect 100 per cent of the controls to die Certainly they should all have very definite shock symptoms, especially the striking temperature drop characteristic of sub-acute shock On the other hand, not all of the treated animals need survive, but a statistically significant proportion of them should show definitely less shock than the controls It also seems probable that in testing agents of possible clinical application the more delicate methods of skin tests, or Friedberger's method of measuring temperature changes would be more important than work with lethal or multiple lethal doses of antigen There might conceivably be quantitative differences, as previously indicated, which this more crude method would mask It is also possible that many agents totally unable to inhibit shock with lethal doses of antigen would be of definite value in protecting against a degree of shock comparable to that found clinically Of the agents studied to date, those which have shown some evidence of inhibitory action might be worthless under other conditions, and those agents which have seemed to exert no protective action might be shown to be of definite value when tested by more delicate methods

In summarizing the findings for discussion, we have placed the experiments in different categories, as follows

I. Those in which efforts have been made to modify the antigen to be used for shock
   A In vitro treatment of the antigen
   B In vivo treatment of the antigen
II Those in which efforts have been made to influence the reacting substances or tissues of the experimental animal

A Treatment before sensitization
B Treatment during sensitization
  1 Treatment early in the sensitization period
  2 Treatment throughout the sensitization period
  3 Treatment late in the sensitization period
C Treatment simultaneously with the second injection of antigen
D Treatment after the second injection of antigen
E Treatment both before and during sensitization
F Treatment both during sensitization and after the second injection of antigen

I A THE IN VITRO TREATMENT OF THE ANTIGEN

A large number of chemical and physical agents have been used in an effort to change the antigen used for the shocking dose, but, in general, there has been very little work done on any one method of inhibition

MATERIAL AND PHYSICAL MEANS USED IN VITRO TO MODIFY THE ANTIGEN TO BE USED FOR SHOCK

Chemical	Hydrochloric acid	*Physical means*
Adrenalin	Hydrogen peroxide	Ageing
Alcohol	Iodine	Dialysis
Ammonium sulphate	Peptone	Drying
Animal charcoal	Pilocarpin	Filtration
Butyric acid	Potassium permanganate	Freezing
Calcium acetate	Sodium citrate	Heating
Cholesterol	Sodium formaldehyde sulphoxylate	Ultra violet light
Eserine	Sodium hyposulphite	X-ray
Ether	Succinic acid peroxide	*Enzymes*
Gelatin	Trikresol	Pancreatin
Glucose	Urethane	Pepsin
Gastric juice		

Glucose, gelatin, peptone, cholesterol, ether, enzymes and a number of miscellaneous substances grouped under "Chemicals," have been mixed in various ways with the antigen Where a clear solution has resulted the mixture has been used for the second dose of antigen and where a precipitate has been formed, the filtrate has been injected Needless to say, an assorted group of alleged antigens has been injected Much of this work was done by Anderson and Rosenau many years ago in their fundamental studies of anaphylaxis Their shocking dose was almost always given intraperitoneally in from 3 to 6 cc amounts This renders the evaluation of their negative results

difficult as in other series they were able to shock sensitized animals with as little as 0 1 cc of antigen given intraperitoneally The antigen used by Rosenau and Anderson was usually horse serum They mixed antigen with varying amounts of alcohol, butyric acid, calcium citrate, hydrogen peroxide, iodine, potassium permanganate, sodium citrate, succinic acid or trikresol Of these mixtures the results from the injection of the alcoholic and hydrogen peroxide filtrates into a very small number of guinea pigs (2 or 3) demonstrated fairly good inhibition of shock The fact that the other mixtures have negative results within the limits of the experiment is not evidence that they are without value under other circumstances The amounts of filtrate or of mixture used were greatly in excess of the amount of untreated antigen needed to shock the controls

Within the limits of the small number of animals used, there is evidence that Carpani, also Surányi and Jarno, working with cholesterol mixtures, Brodin and Huchet using sodium formaldehydesulphoxylate, a drug closely related to novarsenobenzol, and Von Dungern and Hirschfeld, using iodine, were able to inhibit shock

Pancreatin and pepsin were used by Lesné and Dreyfus, who stated that they were able to obtain inhibition, but gave no protocols

Using excised muscle strips, Larsen and his co-workers were able to prevent contraction by immersing the sensitized tissue in from 8 to 10 per cent peptone solutions before the addition of the antigen

No inhibition was obtained by other chemical agents It is interesting to speculate upon the changes produced in the antigen by some of the substances used Some, such as glucose, probably act only as diluents Others precipitate the proteins and so modify them that it is not surprising that no shock is obtained This in no way represents desensitization and should not be accepted as such unless a subsequent injection of untreated antigen is without marked effect or causes definitely less shock than in the controls Where the chemical employed unites with the antigen to form complex sustances quite different from the original antigen, shock obtained with such modifications may be due to something of the nature of an anaphylatoxin In some cases it is impossible to tell whether the action of the agent is upon the antigen or upon the sensitized animal Furthermore in cases where the antigen has been precipitated, some quantitative

comparison should be made by sensitizing fresh animals with the modified antigen before like doses of the modified and unmodified antigens are assumed to be equal

Experimental work on the various changes produced by physical means, such as ageing, dialysis, drying, filtration, freezing, heating, x-ray and ultra violet radiation is of interest There is strong evidence that heating to 55° to 60°C. for an hour will markedly reduce the toxicity of a serum antigen No conclusive work has been done to demonstrate any great change in the antigen by other physical agents However the effect of ultra violet light may be significant and experiments with it should be repeated The interesting work of Giaume would have been more valuable had he shown that his animals which had no shock when given serum irradiated with ultra violet light were then not susceptible to being shocked by the untreated antigen Without this test he has shown no inhibition of specific shock

It is quite possible that ageing, dialysis, drying, filtration and heating simply reduce the toxicity of the antigen Therefore any inhibitory results obtained should be recognized as partial specific desensitization

I B IN VIVO MODIFICATION OF THE SHOCKING DOSE OF ANTIGEN

Most interesting experiments have been done in which a drug was given intravenously to the animal which was later bled to obtain the shocking dose of serum With both arsenobenzene and ink some evidence has been given that the serum so treated in vivo is less toxic than the untreated serum Again it seems to us that the proof of inhibition of specific shock would have been the subsequent injection of unmodified antigen Further experiments along this line, however, using many different agents, might be of the greatest interest, offering as they do innumerable possibilities of variations in time and drug dosage Such experiments more closely approximate the conditions under which the agents would normally be employed than do in vitro tests, and serve to indicate whether or not such inhibitory action might be expected in vivo, although they as yet throw no light on how drugs might be expected to act It is obvious that the ability or inability of a drug to modify in this way the toxicity of an antigen is only half of the story, but it would be of value to know whether or not the action

of certain drugs was upon the antigen or upon the sensitized animal This method of experimentation offers the possibility of determining part of the answer to this question

II A TREATMENT OF THE EXPERIMENTAL ANIMAL BEFORE SENSITIZATION

With the exception of some x-ray radiation all the treatment in this division falls under the head of operative surgery

Adrenalectomy, thymectomy and splenectomy have been performed on unsensitized animals by various workers The removal of the organs in no way affected the later sensitization and shock of the animal

Lanzenberg and Képinow and later others have shown quite conclusively that thyroidectomy on the unsensitized animal will in a rather marked degree lessen his ability either to develop sensitization or to react to a second injection of antigen Control animals were all shocked

Von Heinrich gave an erythema dose to guinea pigs on the day of sensitization Twenty-one days later they survived the shocking dose while the two controls died It is too bad that this original work was not better controlled He also carried out an interesting experiment in passive sensitization Two guinea pigs were irradiated three weeks after sensitization Their serum was transferred to normal animals They had no shock when given amounts of antigen fatal for two controls

II B, 1, 2 AND 3 TREATMENT DURING THE PERIOD OF SENSITIZATION

In this section three sub-groups have been made, some of which overlap unavoidably

MATERIALS OR PHYSICAL MEANS USED TO MODIFY THE REACTING SUBSTANCES OR TISSUES OF THE ANIMAL DURING OR AFTER THE SENSITIZING PERIOD

Surgical	*Colloids*	*Proteins*
Brain surgery	Agar	*Albumose*
Nephrectomy	Congo red	Anaphylatoxin
Splenectomy	Kephalin	Cacosan
Surgical interference	Dextrin	Heparin
Thymectomy	India ink	Hirudin
Thyroidectomy	Saccharated iron oxide	Novoprotein
Vagotomy	Thorium	Peptone

cascosan, peptone, seed extracts, serum fractions (albumin, globulin, euglobulin), normal sera, and whey protein comprise the important ones All of these materials have shown some ability to decrease or inhibit the amount of shock in the sensitized animal However for reasons such as lack of control animals, failure to titrate the effective shocking dose of antigen, paucity of experimental animals, varying dosages spread over a series of animals in groups of one or two, and others, sufficient positive or negative evidence has not been adduced

There has been an enormous amount of work done upon the possible inhibitory effects of serum fractions, and of whole heterologous and homologous sera In each group there is evidence which points toward the inhibitory effect of these agents However, in each group there is an occasional well controlled experiment which shows no inhibition Also there is, we regret to say, a great deal of worthless work It is important that conclusive experiments be carried out in this field

Cascosan has been but little used, and the conclusions in regard to it need corroboration Peptone has caused much discussion as an inhibitor of shock There are well controlled investigations on both sides of the question Whey protein may very possibly inhibit shock but the statement cannot be made from the small number of animals tested

Enzymes No work worthy of consideration has been done Pancreatin and pepsin have been used on only one or two animals

Carbohydrates. In spite of the careful work on glycogen the results obtained were inconclusive

Narcotics Under this heading as well as under others, much work has been reported which must be taken on faith or on authority. General statements and broad assertions are made that such an agent does or does not inhibit shock There is, however, no mention of details

The investigations with chloral hydrate have been for the most part well conducted and present definite evidence of inhibition of shock

Chlorolose, morphine, opium, and paraldehyde, have been reported very incompletely No conclusion can be gained from the reports

There has long been a belief, mainly, we fear, founded on authority, that ether as a narcotic will inhibit shock Besredka first made the

statement A few other investigations yielded affirmatory or contradictory findings Strangely enough we can only find one investigator who has thought it advisable to present his protocols His results are inconclusive

We cannot find that inhalations of chloroform have been used as an anti-anaphylactic agent

Fats Many of the substances of this sort which have been studied, have been used with the idea of lowering surface tension and thereby inhibiting shock

Antitrypsin has been used by Jobling and Petersen They have brought evidence which they considered to indicate that the acetone insoluble part of egg yolk is similar to antitrypsin In a very small number of control and experimental animals they were able to show that the amount of shock was diminished by injection of antitrypsin just before the shocking dose

Cholesterol and lecithin have been investigated at length, but not sufficiently to demonstrate clearly the inhibitory effects of either of these agents Most investigators believe that they have some evidence of inhibition but none of them considers the matter settled

Lanolin may or may not be efficacious as we could only read the abstract taken from a Japanese journal A general statement is made about saponin Sodium oleate would seem to be a very suitable agent to use The work done inclines one to believe that inhibition may be obtained if the proper sequence of dosage and time be worked out

Chemicals Among this mass of agents, salts, acids, bases and one oil, we have found seven substances by means of which the investigators have been definitely able to inhibit shock within the limits of the experiment Barium chloride, barium sulphate, benzol, certain mineral waters, sodium bicarbonate, sodium sulphate and sodium chloride, have all been used, mineral waters and sodium chloride have been studied quite extensively In order to protect the animal by the latter it must be given in such large doses that sickness and death frequently result from the therapeusis

The investigations of guanidine and neoarsphenamine have been good but corroboration is needed before definite proof of inhibition is to be accepted

Almond oil injected just before the second dose of antigen has been used with inconclusive results

The amount of work done with atropin is large It is described under this heading as the best results, i e , in preventing shock, are obtained when it is given just before the second injection of antigen Well controlled investigations have given results which satisfactorily demonstrate the ability of this drug to inhibit shock

The investigations with chloride or sulphate of barium, with Bayer 205 and with narcotics have been described Those with manganese chloride, sodium nitrite, tallhamine, adrenalin and pilocarpin are inconclusive

Oxygen inhalations and stovain intravenously seem to give some inhibition, but the subject needs further study

The physical methods used such as lowering of barometric pressure and chilling protected a certain number of the animals, x-ray radiation was given without effect

II D TREATMENT AFTER THE SECOND INJECTION OF ANTIGEN

It is very difficult to evaluate the investigations falling within this group In the first place little has been done, adrenalin and urethane have been used in combination, potassium permanganate was tested on only one animal; tallhamine was tested on a small number and may have prolonged life The work on calcium chloride is equally inconclusive Some of these substances may give protection, but none has been definitely demonstrated

II E TREATMENT BEFORE AND DURING SENSITIZATION

In this group are included x-ray, trypan blue and starvation, none of which gave definite protection

SUMMARY OF AGENTS INHIBITING ANAPHYLAXIS

After analysis of the protocols of the studies reported in the addenda, we have summarized those agents for which conclusive evidence of the inhibition of anaplylactic shock has been presented Our criteria have included the number of controls, the number of treated animals, and the titration of the antigen We have not included in this list agents which have been reported without careful protocols This does

not mean that such work is necessarily unsound, but without such protocols it has been impossible to make accurate analyses of the experiments With these restrictions in mind we have collected from the records in the addenda the agents for which there is conclusive evidence of inhibitory action These are presented in the following list

AGENTS FOR WHICH THERE IS CONCLUSIVE EVIDENCE OF INHIBITORY ACTION

1 Atropine, given before the second injection of antigen
2 Barium chloride, given before, or added to, the second dose of antigen
3 Barium sulphate, given after the second injection of antigen
4 Reduction of barometric pressure, after the second injection of antigen
5 Benzol in large doses, before and during sensitization
6 Trephination before the second injection of antigen
7 Calcium chloride with and after the second injection of antigen (Clinical use)
8 Chloral hydrate before the second injection of antigen
9 Heating of the serum antigen
10 Heparin before the second injection of antigen
11 Intercurrent infection with tuberculosis
12 Saccharated iron oxide during the sensitization period
13 Mercurochrome 220
14 Milk (aolan)
15 Certain mineral waters during the sensitization period
16 Multiple sensitization and treatment with one of the several antigens
17 Sodium bicarbonate before the second injection of antigen
18 Sodium carbonate before the second injection of antigen
19 Sodium chloride before the second injection of antigen
20 Sodium formaldehyde sulphoxylate, added to the second dose of antigen

At this time there is too little knowledge of the exact method of action of this diversified group of 18 agents to allow conclusions of any value to be drawn from them It should also be remembered that their efficiency can be recognized only within the definite limits of the investigative work

There are a number of agents concerning which there is incomplete but possible evidence of inhibitory action These agents are presented in the following list

AGENTS FOR WHICH THERE IS INCOMPLETE BUT POSSIBLE EVIDENCE OF INHIBITORY ACTION

1 Adrenalin, before and after the second injection of antigen
2 Alcohol treatment of the serum antigen
3 Allocaine before the second injection of antigen
4 Ammonium sulphate precipitation of the serum antigen

5 Anaphylatoxin, given before the second injection of antigen
6 Antitrypsin, given before the second injection of antigen
7 Arsenobenzene, injected intravenously into animals later bled to supply the second dose of antigen
8 Chloroform, given intravenously before the second injection of antigen
9 Cholesterin, before or added to the second dose of serum antigen
10 Cholin Hydrochloride before the second dose of antigen
11 Complement fixation, before the second dose of antigen
12 Egg fat, before the second dose of antigen
13 Ether, given intravenously before the second dose of antigen
14 Hydrogen peroxide treatment of the antigen
15 Ink, during sensitization, or given animals later bled to supply the second dose of antigen
16 Iodinization of the serum antigen
17 Kephalin, before the second injection of antigen
18 Lecithin, before the second injection of antigen
19 Manganese chloride, before the second injection of antigen
20 Neoarsphenamine, in passive anaphylaxis
21 Oxygen, before the second injection of antigen
22 Peptone, before the second injection of antigen
23 Pilocarpine hydrochloride, before or with the second dose of antigen
24 Pregnancy
25 Roentgen ray
26 Seed extracts
27 Serum fractions
28 Serum globulin
29 Serum, normal
30 Sodium hyposulphite with the second dose of antigen
31 Sodium iodoxybenzoate, before the second injection of antigen, in skin tests
32 Sodium oleate
33 Starvation
34 Temperature reduction of the sensitized animal before shock
35 Thyroidectomy
36 Thyroid extract in small amounts by mouth two days before shock
37 Ultra-violet light irradiation of the serum antigen used for shock.
38 Urine from anaphylactic animals
39 Vagotomy, before the second injection of antigen
40 Vitamine C deficiency during sensitization
41 Whey, given before the second injection of whole milk.

SUMMARY OF AGENTS WHICH INTENSIFY SHOCK

Among the agents that intensify shock we find a number which also may inhibit it, depending usually upon the dosage Intercurrent infection, which apparently may either intensify or diminish shock, acts in an entirely unknown manner.

AGENTS FOR WHICH THERE IS SOME EVIDENCE OF INTENSIFYING ACTION

1 Adrenalectomy, before the second injection of antigen
2 Benzol, in small doses before and during sensitization
3 Heterophile antigen, before the second injection of antigen
4 Intercurrent infection during sensitization, or before sensitization
5 Quinine, before the second injection of antigen
6 Sodium citrate, before the second injection of antigen
7 Sodium persulphate, before the second injection of antigen
8 Thyroid gland extract by mouth, in large amounts, before the second injection of antigen
9 Trypan blue
10 Vitamine B deficiency during the sensitization period
11 Mud from Hot Springs

THEORIES TO EXPLAIN MODE OF ACTION OF INHIBITING AGENT

The theory most in vogue at present is that of *changes of colloidal* equilibrium Such changes, involving an increased viscosity and lowered surface tension of the blood, have been shown to have been brought about by certain mineral waters and by ether or chloroform given intravenously It seems probable also that many of the agents studied cause such changes, although they have not been studied from this point of view

The theory of *reticulo-endothelial block* has been advanced by various investigators working with ink, saccharated oxide of iron, lanolin and other agents Such block is supposed to work in one of two ways, first, by plugging the reticulo endothelial system *before* the first administration of antigen, and second, by blocking the reticulo-endothelial system of the sensitized animal and therefore preventing shock There is, however, no authoritative evidence that these agents do inhibit shock, nor that, should they protect, that they would do so by such a blockade Furthermore, there is no evidence that it is possible to blockade the reticulo endothelial cell completely

The theory of *exhaustion of antibodies by a non-specific protein* is comparable to that observed in vitro in complement fixation Under this group may be listed intercurrent infection, the injection of heterologous sera, of peptone, of anaphylatoxins, of serum fractions, of whey protein, or sensitization with several antigens Intercurrent infection is the only one of these agents which has been definitely proven to inhibit shock except for multiple sensitization and treat-

ment with one of the antigens This theory is entirely unproved and these agents may act in some other, as yet unknown way

The theory of *neurogenic action* may be utilized to explain the diminution of anaphylactic shock in guinea pigs brought about by the use of atropine and adrenalin There is definite knowledge that atropine will inhibit shock in guinea pigs and probably this is by its action on the vagus Adrenalin has not been definitely shown to inhibit shock, but in the experiments recorded, the action may be interpreted as being due to the direct action of the drug on the sympathetic system The action of chloroform and of ether as anesthetics is entirely unknown

Action by a *modification of antibody production* is of particular interest because it may be stretched to cover almost any body reaction Of the agents which have been found to have some such probable inhibition, 3 varieties are found

First, such agents as benzol, which is thought by some to have a direct action on antibody production

Second, agents generated within the body itself as a result of metabolic changes, as for example, vitamin B or C deficiency, starvation or pregnancy

Third, agents which produce changes indirectly in antibody production, as by the removal of certain organs Thyroidectomy has been conclusively shown to decrease markedly the ability of the animal so treated before sensitization to respond with the same degree of shock as the controls

A number of agents have been used because they in themselves *induce shock in some way similar to anaphylactic shock* Peptone, anaphylatoxins, urine from guinea pigs that have had anaphylactic shock, are examples of such agents No conclusive work has been done to show that any protection obtained with such agents is due to their shocking properties

On the other hand, a number of agents have been tried because they *produce results opposite* to those found in anaphylactic shock Chief of these are substances which increase the blood pressure, such as barium chloride and adrenalin, drugs which relax the bronchial muscles, such as atropine or adrenalin, and agents, such as the narcotics, which affect the central nervous system Lowering of the

barometric pressure has also been used because it produces results which are, as a whole, opposed to the effects of anaphylactic shock. Starvation has been used because of its accompanying leucopenia, which was supposed to offset the leucocytosis observed in shock.

Certain other theories have been advanced of which there is even less conclusive support than for those just discussed. Among this last group are agents which *exhaust complement*, which *increase the blood volume*, as in pregnancy or the administration of sodium chloride, or *saturate the precipitable elements of the blood* as barium sulphate. The theory of modifying the specific nature of the antigen has been discussed previously. It is futile to enter into detail in regard to these theories, as not one has been proved, their very diversity signifying how utterly confused has been the entire problem.

In summary, we know of no facts or any theory which will explain conclusively the definite non-specific inhibition of anaphylactic shock that is produced by a variety of agents. It is well worth the endeavor of chemists, physicists, physiologists, immunologists and clinicians to throw further light upon this problem.

ADDENDA

Discussion of Agents, in Alphabetical Order

Acetone

Surányi and Jarno, in 1928, obtained no inhibition of shock when the serum used for the second injection had been treated with acetone. All five of the animals given treated serum died, as well as the five guinea pigs given normal serum. These experiments were controls for more successful tests with cholesterinized serum.

Adrenalectomy

Képinow, in 1922, found that upon the removal of the suprarenal tissue, guinea pigs could be killed by 0.025 cc. of serum, whereas the controls required 0.1 cc. The number of controls was not stated. This is one of the rare instances of apparent intensification of shock.

Adrenalin

Anderson and Schultz in 1909 made an exceptionally well controlled study of the action of this drug in experimental anaphylaxis. Thirty days after intraorbital sensitization, guinea pigs were treated before the second injection of anti-

gen, probably given intravenously The exact interval between treatment and shock was not stated No animals were treated with adrenalin alone, the drug being given intraperitoneally simultaneously with the intravenous administration of chloral hydrate and urethane, or with artificial respiration with oxygen, or with all three The results may be summarized as follows

TREATMENT	TOTAL	DIED	LIVED	
			Number	Per cent
Adrenalin, chloral hydrate and urethane	12	7	5	41
None	12	10	2	16
Adrenalin, chloral hydrate and urethane, and artificial respiration with oxygen	12	4	8	66 6
None	13	11	2	15
Artificial respiration only	16	9	7	43
None	16	13	3	18

Unfortunately, owing to the combined treatment, the exact rôle of the individual agents cannot be determined Certainly the best results were obtained by treating with all four In every series the difference between the treated animals and the controls was striking This is one of the few papers in which combined treatment was given, a field which offers unlimited opportunity for further study

In 1918 *Pelz and Jackson*, sensitized dogs with 3 injections of horse serum, or of egg white It was found that adrenalin was of value if given early after the shocking dose of antigen, but of no value if not given until the spasm had thoroughly developed The experiments were not comparable to those in which treatment preceded the shocking dose of antigen

Hanzlik and Karsner in 1920, studying the action of adrenalin in shock from many different substances, reported a few experiments with serum anaphylaxis No untreated controls were given for these particular experiments In all, only 4 sensitized guinea pigs were treated with adrenalin, given intravenously either just before, with, or after the shocking dose of antigen Two animals died and 2 survived after shock, with marked dyspnoea Nevertheless, the authors concluded that "when injected together with the antigen or immediately preceding it, epinephrine in the dosage of 0 0005 cc of 1 10,000 per gram of body weight intravenously prevents death from true anaphylactic shock in guinea pigs " For obvious reasons, such conclusions do not seem justified by the evidence presented in the paper

Galambos, in 1913, treated serum-sensitized guinea pigs with intravenous adrenalin before the second injection of antigen by the same route The lethal doses of antigen and of adrenalin were determined In all, 12 animals received $\frac{1}{10}$ mgm of adrenalin, followed by multiple lethal doses of antigen from 15 to 75 minutes

later In many instances, only one animal was used for each variation of antigen and of time interval In general, however, there was evidence that protection might be obtained with adrenalin against 3, or rarely more, lethal doses of antigen The authors also seemed justified in concluding that the time of treatment was important Too few experiments were done with other dosages to warrant any conclusions, including one experiment in which both atropine and adrenalin were given

Levy Solal and Tzanck in 1923 failed to save either of 2 guinea pigs by adding non lethal doses of adrenalin to the shocking dose of serum, given intracardially Not only was the series negligibly small, but no determination of the lethal dose of antigen was made The amount given, 1 cc , from which all of the controls died, probably represented many lethal doses These authors cited without reference the work of Garrelon, Santenoise and Tirrel, which we have been unable to trace

Summary (1) No conclusive evidence is offered by Hanzlik and Karsner, nor by Levy Solal and Tzanck that adrenalin modifies shock when combined with the second dose of antigen

(2) Some evidence, not wholly convincing, has been presented by Galambos to show that adrenalin alone may protect when given before the shocking dose of antigen Anderson and Schultz combined adrenalin with other treatment, so that the exact rôle of the adrenalin could not be determined

(3) Some protective action of adrenalin, given dogs soon after the shocking dose of antigen, has been shown by Pelz and Jackson

Agar

Besredka, in 1920, failed to inhibit shock by giving agar intravenously This paper, which gave no protocols, is discussed under "Anaphylatoxin" It is inconclusive

Aging of antigen

Besredka, in 1907 b, found that although the act of aging serum diminished its toxicity, some shocking effect could be obtained even with a 13 year old sample

Rosenau and Anderson, in 1908, however, found sera from 2 to 118 days old markedly toxic

Although this aging of the antigen is obviously closely related to specific desensitization, it is cited here as an instance of attempted modification of the antigen

Albumoses

Heyde, in 1912, obtained no modification of shock by treating serum sensitized animals with albumoses 3 days before shock Although no protocols were given the work seems to have been adequate controlled

Alcohol

Rosenau and Anderson, in 1906, treated 25 cc of serum with from 5 to 10 cc of 95 per cent alcohol The mixture was kept at 15°C for 40 hours and then filtered Two sensitized guinea pigs which received 6 cc of this filtrate intraperitoneally died, as well as the animals receiving the same amount of untreated serum Three animals survived the injection of 3 cc of the treated serum Other controls given 0 1 cc of the untreated serum died, so that 3 cc represented about 30 lethal doses

Besredka, in 1908, stated that he obtained inhibition of shock by the narcotic effect of alcohol No protocols were given

Allocaine

Lumière and Enselme, in 1926, treated sensitized guinea pigs intravenously with 2 5 mgm of allocaine in 0 5 per cent solution and found that they then resisted amounts of antigen lethal for an unstated number of controls

Almond oil

Achard and Flandin, in 1911, obtained no inhibition of shock by giving from 5 to 20 cc of almond oil just before shock The experiments were not conclusive

Ammonium sulphate

Rosenau and Anderson, in 1906, obtained questionable inhibition of shock by precipitation of the serum antigen with ammonium sulphate Subsequent dialysis removed the sulphate and other inorganic salts Six cubic centimeters of this filtrate injected intraperitoneally caused death in 1 guinea pig, 5 cc killing 1 of 2 Controls were killed with 6 cc of untreated serum This antigen dosage was high, because the authors showed that 0 1 cc of serum usually killed susceptible animals

Anaphylatoxin

Lurà, in 1912, failed to inhibit shock by treating 2 sensitized guinea pigs with Bacillus prodigiosus anaphylatoxin, given intraperitoneally 24 hours before shock with 1 lethal dose of antigen Although both untreated controls and anaphylatoxin controls were used, no conclusions can be drawn from so small a series

Aronson, in 1912, gave sensitized guinea pigs sub-lethal doses of Bacillus prodigiosus anaphylatoxin intravenously 1 day before the second injection of the antigen All of the treated animals lived and all of the untreated animals died Their number was not given

Besredka, in 1920, made a general statement that sensitized animals, treated intravenously with suspensions of agar, were not protected against a minimum lethal dose of antigen

Dale and Kellaway, in 1923, concluded that "acquired tolerance to anaphylatoxin does not involve desensitization of the anaphylactic animal, nor does specific

desensitization involve tolerance to anaphylatoxin" This seems to have been clearly shown for both passively and actively sensitized guinea pigs, when the second injection of antigen followed from 3 to 25 minutes after the administration of anaphylatoxin However, when the shocking dose of antigen was not given until 2½ hours after the injection of anaphylatoxin, none of the 3 animals so treated had shock In another series anaphylatoxin immune serum failed to protect 1 animal shocked 5 minutes after treatment But because normal serum also partially protected 1 animal shocked 70 minutes after treatment, the authors concluded that the protection obtained by the immune serum was not due to its immune qualities It is unfortunate that in these carefully controlled and beautifully planned experiments, much larger series of test animals were not used

Summary In spite of the importance which this aspect of the problem would seem to have upon the relation of anaphylatoxin shock and anaphylactic shock, there is no conclusive evidence as to whether anaphylatoxin shock does or does not inhibit anaphylactic shock Further studies along this line, with some quantitative determination of the amount of protection obtained, if any, would certainly be of interest Protection with anaphylatoxin against anaphylactic shock, however, would not be proof of the identity of the two types of shock

Animal charcoal

Besredka, in 1907, found that contact of the serum antigen with animal charcoal did not reduce the toxicity of the serum

Antitrypsin

The question of changes in the antitrypsin content of serum in anaphylactic shock involves many complexities

Seligmann, in 1912, reported investigations showing that the antitrypsin increase in shock was not marked

Ando, in 1913, was also unable to demonstrate any specific increase of antitrypsin in anaphylactic shock, that is, the increase was no greater than after the sensitizing injection of antigen, or after the injection of an heterologous substance

Jobling and Peterson, in 1914, further complicated the question They showed, to their satisfaction, that antitrypsin was an acetone soluble lipoid, which could be obtained from serum or egg yolk, and that the injection of such an extract raised the antitrypic titre of normal serum They concluded that, by treating sensitized animals with the subcutaneous injection of antitrypsin before the second injection of antigen, guinea pigs could be made refractory to shock, because of the increase of antitrypsin in their serum An analysis of the protocols presented makes it difficult to regard the conclusions as entirely justified, on account of the small number of animals used Thus, in the antitrypsin series, of the 3 treated animals, 1 died and 2 lived, while both of the comparable controls died It is possible that in a larger series, some of the controls might have lived, or more of the treated animals have died The results with lipoid free antigen are inconclusive for the

from the lethal effects of 0 1 cc of horse serum antigen per 100 grams of body weight In another set of animals, sensitized to swine serum and given a shocking dose of antigen of 0 3 cc per 100 grams of body weight, 1 of the 6 treated animals lived

Karsner and Nutt, in 1911, approached the problem by determining a constant minimum lethal dose of shocking serum The dosage of atropine was raised until the minimum protective dose was found The shocking dose of serum was then increased and the minimum amount of drug necessary to protect was redetermined This method was continued up to the toxic limits of atropine Both drug and antigen were given intravenously

2 mgm of atropine protected 1 animal against 0 4 cc of serum
2 mgm of atropine protected 1 animal against 0 6 cc of serum
7 mgm of atropine protected 1 animal against 0 8 cc of serum
25 mgm of atropine protected 1 animal against 1 0 cc of serum

Protocols were not given for the controls, but the results of Karsner and Nutt were sufficiently definite to be of great value

Galambos in 1913, gave 1 animal for each variation different amounts of atropine at different times before multiple lethal doses of shocking antigen Although controlled, the experiments are difficult to evaluate and in our opinion the author has little justification for his conclusions that atropine does protect, and that the time of treatment and dosage are important

Pelz and Jackson, in 1918, working with dogs, found that atropine was of no value if given after the shocking dose of antigen

In *1920 Hanzlik and Karsner* treated two serum-sensitized guinea pigs with atropine, 3 and 5 mgms No controls were given, but the authors concluded that atropine could partially protect against serum shock This conclusion hardly seems justified from the experiments cited

Levy-Solal and Tzanck, in 1923, in uncontrolled experiments, found that animals had slight or no shock when atropine was given with the shocking dose of antigen

Stoland and Sherwood, in 1923, using the excised, sensitized, uterine muscle of virgin guinea pigs and 1 per cent solutions of atropine, found that the response of the sensitized muscle to the specific antigen was prevented by atropine Larger doses of atropine did not increase the muscle tone so much as small ones

Zunz and LaBarre, in 1924, found that 1 mgm of atropine per 100 grams of weight prevented anaphylactic shock if given intraperitoneally to sensitized animals 20 to 35 minutes before the intravenous injection of 1 minimum lethal dose, or slightly more, of antigen In the treated animals that were completely protected, the surface tension and reaction of the blood remained normal From 0 25 to 0 5 mgm of drug per 100 grams did not protect and the surface tension and hydrogen ion concentration of the blood were diminished as in the controls It is unfortunate that the authors did not present protocols of either controls or of the treated animals

Summary The work of any value which has been done that tends to show the favorable effect of atropine on anaphylaxis is small Auer's experiments are good,

but he did not repeat his only successful one Karsner and Nutt have shown that some protection can be obtained The reports by Biedl and Kraus and by Zunz and La Barre contain no protocols

On the other hand, there are three well controlled investigations by Mita, by Friedberger, and by Anderson and Shultz, which show no evidence of the effectiveness of atropine in allaying shock

The work of Stoland and Sherwood, well done though it is, seems of questionable value inasmuch as we do not know that *in vitro* effects can be interpreted as similar to those occuring *in vivo*

The outstanding factor in favor of the correctness of Auer's work is that he used larger doses than those who were unable to corroborate his work To this one must add the quite conclusive work of Karsner and Nutt showing that large amounts of atropine are necessary to protect against increasing amounts of the shocking dose of antigen

Barium chloride

Biedl and Kraus, in 1909, employed barium chloride in dogs Although no protocols or dosages were given, the authors concluded that after the blood pressure of sensitized dogs had been raised with barium chloride, the subsequent administration of a shocking dose of antigen failed to cause the drop in blood pressure characteristic of anaphylactic shock Even when treatment was not given until after shock, when the blood pressure had reached its lowest level, a rise of pressure could be obtained with barium chloride

Pfeiffer and Jarisch, in 1913, working with guinea pigs, found that barium chloride gave definite protection when injected intraperitoneally in doses from 0 005 to 0 05 gram, 30 minutes before the intraperitoneal injection of the shocking dose of antigen These experiments were well controlled They are not strictly comparable to those of other workers, who used lethal doses of antigen, as Pfeiffer and Jarisch gave doses of antigen small enough to allow a study of temperature changes in mild shock Other experiments in this same paper, however, are comparable, and showed that protection was obtained when 0 004 gram of barium chloride were given before the intravenous injection of the shocking dose of antigen In other experiments, barium chloride was added to the shocking dose of antigen, in the proportion of 8 7 cc of serum and 1 3 cc of a 10 per cent solution of the drug Two cubic centimeters of this mixture protected the 6 treated animals Four controls died

Summary The work of Biedl and Kraus cannot be evaluated on account of the lack of details The study of Pfeiffer and Jarisch offers valid evidence that anaphylactic shock can be inhibited with barium chloride, given either before or with the shocking dose of antigen

Barium sulphate

Lumière and Couturier, in 1921 a showed that the intracardial injection of 0 5 cc of 0 265 per cent emulsion of barium sulphate, given just before the intracardial

from the lethal effects of 0 1 cc of horse serum antigen per 100 grams of body weight In another set of animals, sensitized to swine serum and given a shocking dose of antigen of 0 3 cc per 100 grams of body weight, 1 of the 6 treated animals lived

Karsner and Nutt, in 1911, approached the problem by determining a constant minimum lethal dose of shocking serum The dosage of atropine was raised until the minimum protective dose was found The shocking dose of serum was then increased and the minimum amount of drug necessary to protect was redetermined This method was continued up to the toxic limits of atropine Both drug and antigen were given intravenously

2 mgm of atropine protected 1 animal against 0 4 cc of serum
2 mgm of atropine protected 1 animal against 0 6 cc of serum
7 mgm of atropine protected 1 animal against 0 8 cc of serum
25 mgm of atropine protected 1 animal against 1 0 cc of serum

Protocols were not given for the controls, but the results of Karsner and Nutt were sufficiently definite to be of great value

Galambos in 1913, gave 1 animal for each variation different amounts of atropine at different times before multiple lethal doses of shocking antigen Although controlled, the experiments are difficult to evaluate and in our opinion the author has little justification for his conclusions that atropine does protect, and that the time of treatment and dosage are important

Pelz and Jackson, in 1918, working with dogs, found that atropine was of no value if given after the shocking dose of antigen

In *1920 Hanzlik and Karsner* treated two serum-sensitized guinea pigs with atropine, 3 and 5 mgms No controls were given, but the authors concluded that atropine could partially protect against serum shock This conclusion hardly seems justified from the experiments cited

Levy-Solal and Tzanck, in 1923, in uncontrolled experiments, found that animals had slight or no shock when atropine was given with the shocking dose of antigen

Stoland and Sherwood, in 1923, using the excised, sensitized, uterine muscle of virgin guinea pigs and 1 per cent solutions of atropine, found that the response of the sensitized muscle to the specific antigen was prevented by atropine Larger doses of atropine did not increase the muscle tone so much as small ones

Zunz and LaBarre, in 1924, found that 1 mgm of atropine per 100 grams of weight prevented anaphylactic shock if given intraperitoneally to sensitized animals 20 to 35 minutes before the intravenous injection of 1 minimum lethal dose, or slightly more, of antigen In the treated animals that were completely protected, the surface tension and reaction of the blood remained normal From 0 25 to 0 5 mgm of drug per 100 grams did not protect and the surface tension and hydrogen ion concentration of the blood were diminished as in the controls It is unfortunate that the authors did not present protocols of either controls or of the treated animals

Summary The work of any value which has been done that tends to show the favorable effect of atropine on anaphylaxis is small Auer's experiments are good,

but he did not repeat his only successful one Karsner and Nutt have shown that some protection can be obtained The reports by Biedl and Kraus and by Zunz and La Barre contain no protocols

On the other hand, there are three well controlled investigations by Mita, by Friedberger, and by Anderson and Shultz, which show no evidence of the effectiveness of atropine in allaying shock

The work of Stoland and Sherwood, well done though it is, seems of questionable value inasmuch as we do not know that *in vitro* effects can be interpreted as similar to those occuring *in vivo*

The outstanding factor in favor of the correctness of Auer's work is that he used larger doses than those who were unable to corroborate his work To this one must add the quite conclusive work of Karsner and Nutt showing that large amounts of atropine are necessary to protect against increasing amounts of the shocking dose of antigen

Barium chloride

Biedl and Kraus, in 1909, employed barium chloride in dogs Although no protocols or dosages were given, the authors concluded that after the blood pressure of sensitized dogs had been raised with barium chloride, the subsequent administration of a shocking dose of antigen failed to cause the drop in blood pressure characteristic of anaphylactic shock Even when treatment was not given until after shock, when the blood pressure had reached its lowest level, a rise of pressure could be obtained with barium chloride

Pfeiffer and Jarisch, in 1913, working with guinea pigs, found that barium chloride gave definite protection when injected intraperitoneally in doses from 0 005 to 0 05 gram, 30 minutes before the intraperitoneal injection of the shocking dose of antigen These experiments were well controlled They are not strictly comparable to those of other workers, who used lethal doses of antigen, as Pfeiffer and Jarisch gave doses of antigen small enough to allow a study of temperature changes in mild shock Other experiments in this same paper, however, are comparable, and showed that protection was obtained when 0 004 gram of barium chloride were given before the intravenous injection of the shocking dose of antigen In other experiments, barium chloride was added to the shocking dose of antigen, in the proportion of 8 7 cc of serum and 1 3 cc of a 10 per cent solution of the drug Two cubic centimeters of this mixture protected the 6 treated animals Four controls died

Summary The work of Biedl and Kraus cannot be evaluated on account of the lack of details The study of Pfeiffer and Jarisch offers valid evidence that anaphylactic shock can be inhibited with barium chloride, given either before or with the shocking dose of antigen

Barium sulphate

Lumière and Couturier, in 1921 a showed that the intracardial injection of 0 5 cc of 0 265 per cent emulsion of barium sulphate, given just before the intracardial

from the lethal effects of 0 1 cc of horse serum antigen per 100 grams of body weight In another set of animals, sensitized to swine serum and given a shocking dose of antigen of 0 3 cc per 100 grams of body weight, 1 of the 6 treated animals lived

Karsner and Nutt, in 1911, approached the problem by determining a constant minimum lethal dose of shocking serum The dosage of atropine was raised until the minimum protective dose was found The shocking dose of serum was then increased and the minimum amount of drug necessary to protect was redetermined This method was continued up to the toxic limits of atropine Both drug and antigen were given intravenously

2 mgm of atropine protected 1 animal against 0 4 cc of serum
2 mgm of atropine protected 1 animal against 0 6 cc of serum
7 mgm of atropine protected 1 animal against 0 8 cc of serum
25 mgm of atropine protected 1 animal against 1 0 cc of serum

Protocols were not given for the controls, but the results of Karsner and Nutt were sufficiently definite to be of great value

Galambos in 1913, gave 1 animal for each variation different amounts of atropine at different times before multiple lethal doses of shocking antigen Although controlled, the experiments are difficult to evaluate and in our opinion the author has little justification for his conclusions that atropine does protect, and that the time of treatment and dosage are important

Pelz and Jackson, in 1918, working with dogs, found that atropine was of no value if given after the shocking dose of antigen

In *1920 Hanzlik and Karsner* treated two serum-sensitized guinea pigs with atropine, 3 and 5 mgms No controls were given, but the authors concluded that atropine could partially protect against serum shock This conclusion hardly seems justified from the experiments cited

Levy-Solal and Tzanck, in 1923, in uncontrolled experiments, found that animals had slight or no shock when atropine was given with the shocking dose of antigen

Stoland and Sherwood, in 1923, using the excised, sensitized, uterine muscle of virgin guinea pigs and 1 per cent solutions of atropine, found that the response of the sensitized muscle to the specific antigen was prevented by atropine Larger doses of atropine did not increase the muscle tone so much as small ones

Zunz and LaBarre, in 1924, found that 1 mgm of atropine per 100 grams of weight prevented anaphylactic shock if given intraperitoneally to sensitized animals 20 to 35 minutes before the intravenous injection of 1 minimum lethal dose, or slightly more, of antigen In the treated animals that were completely protected, the surface tension and reaction of the blood remained normal From 0 25 to 0 5 mgm of drug per 100 grams did not protect and the surface tension and hydrogen ion concentration of the blood were diminished as in the controls It is unfortunate that the authors did not present protocols of either controls or of the treated animals

Summary The work of any value which has been done that tends to show the favorable effect of atropine on anaphylaxis is small Auer's experiments are good,

but he did not repeat his only successful one Karsner and Nutt have shown that some protection can be obtained The reports by Biedl and Kraus and by Zunz and La Barre contain no protocols

On the other hand, there are three well controlled investigations by Mita, by Friedberger, and by Anderson and Shultz, which show no evidence of the effectiveness of atropine in allaying shock

The work of Stoland and Sherwood, well done though it is, seems of questionable value inasmuch as we do not know that *in vitro* effects can be interpreted as similar to those occuring *in vivo*

The outstanding factor in favor of the correctness of Auer's work is that he used larger doses than those who were unable to corroborate his work To this one must add the quite conclusive work of Karsner and Nutt showing that large amounts of atropine are necessary to protect against increasing amounts of the shocking dose of antigen

Barium chloride

Biedl and Kraus, in 1909, employed barium chloride in dogs Although no protocols or dosages were given, the authors concluded that after the blood pressure of sensitized dogs had been raised with barium chloride, the subsequent administration of a shocking dose of antigen failed to cause the drop in blood pressure characteristic of anaphylactic shock Even when treatment was not given until after shock, when the blood pressure had reached its lowest level, a rise of pressure could be obtained with barium chloride

Pfeiffer and Jarisch, in 1913, working with guinea pigs, found that barium chloride gave definite protection when injected intraperitoneally in doses from 0 005 to 0 05 gram, 30 minutes before the intraperitoneal injection of the shocking dose of antigen These experiments were well controlled They are not strictly comparable to those of other workers, who used lethal doses of antigen, as Pfeiffer and Jarisch gave doses of antigen small enough to allow a study of temperature changes in mild shock Other experiments in this same paper, however, are comparable, and showed that protection was obtained when 0 004 gram of barium chloride were given before the intravenous injection of the shocking dose of antigen In other experiments, barium chloride was added to the shocking dose of antigen, in the proportion of 8 7 cc of serum and 1 3 cc of a 10 per cent solution of the drug Two cubic centimeters of this mixture protected the 6 treated animals Four controls died

Summary The work of Biedl and Kraus cannot be evaluated on account of the lack of details The study of Pfeiffer and Jarisch offers valid evidence that anaphylactic shock can be inhibited with barium chloride, given either before or with the shocking dose of antigen

Barium sulphate

Lumière and Couturier, in 1921 a showed that the intracardial injection of 0 5 cc of 0 265 per cent emulsion of barium sulphate, given just before the intracardial

from the lethal effects of 0 1 cc of horse serum antigen per 100 grams of body weight In another set of animals, sensitized to swine serum and given a shocking dose of antigen of 0 3 cc per 100 grams of body weight, 1 of the 6 treated animals lived

Karsner and Nutt, in 1911, approached the problem by determining a constant minimum lethal dose of shocking serum The dosage of atropine was raised until the minimum protective dose was found The shocking dose of serum was then increased and the minimum amount of drug necessary to protect was redetermined This method was continued up to the toxic limits of atropine Both drug and antigen were given intravenously

2 mgm of atropine protected 1 animal against 0 4 cc of serum
2 mgm of atropine protected 1 animal against 0 6 cc of serum
7 mgm of atropine protected 1 animal against 0 8 cc of serum
25 mgm of atropine protected 1 animal against 1 0 cc of serum

Protocols were not given for the controls, but the results of Karsner and Nutt were sufficiently definite to be of great value

Galambos in 1913, gave 1 animal for each variation different amounts of atropine at different times before multiple lethal doses of shocking antigen Although controlled, the experiments are difficult to evaluate and in our opinion the author has little justification for his conclusions that atropine does protect, and that the time of treatment and dosage are important

Pelz and Jackson, in 1918, working with dogs, found that atropine was of no value if given after the shocking dose of antigen

In *1920 Hanzlik and Karsner* treated two serum-sensitized guinea pigs with atropine, 3 and 5 mgms No controls were given, but the authors concluded that atropine could partially protect against serum shock This conclusion hardly seems justified from the experiments cited

Levy-Solal and Tzanck, in 1923, in uncontrolled experiments, found that animals had slight or no shock when atropine was given with the shocking dose of antigen

Stoland and Sherwood, in 1923, using the excised, sensitized, uterine muscle of virgin guinea pigs and 1 per cent solutions of atropine, found that the response of the sensitized muscle to the specific antigen was prevented by atropine Larger doses of atropine did not increase the muscle tone so much as small ones

Zunz and LaBarre, in 1924, found that 1 mgm of atropine per 100 grams of weight prevented anaphylactic shock if given intraperitoneally to sensitized animals 20 to 35 minutes before the intravenous injection of 1 minimum lethal dose, or slightly more, of antigen In the treated animals that were completely protected, the surface tension and reaction of the blood remained normal From 0 25 to 0 5 mgm of drug per 100 grams did not protect and the surface tension and hydrogen ion concentration of the blood were diminished as in the controls It is unfortunate that the authors did not present protocols of either controls or of the treated animals

Summary The work of any value which has been done that tends to show the favorable effect of atropine on anaphylaxis is small Auer's experiments are good,

but he did not repeat his only successful one Karsner and Nutt have shown that some protection can be obtained The reports by Biedl and Kraus and by Zunz and La Barre contain no protocols

On the other hand, there are three well controlled investigations by Mita, by Friedberger, and by Anderson and Shultz, which show no evidence of the effectiveness of atropine in allaying shock

The work of Stoland and Sherwood, well done though it is, seems of questionable value inasmuch as we do not know that *in vitro* effects can be interpreted as similar to those occuring *in vivo*

The outstanding factor in favor of the correctness of Auer's work is that he used larger doses than those who were unable to corroborate his work To this one must add the quite conclusive work of Karsner and Nutt showing that large amounts of atropine are necessary to protect against increasing amounts of the shocking dose of antigen

Barium chloride

Biedl and Kraus, in 1909, employed barium chloride in dogs Although no protocols or dosages were given, the authors concluded that after the blood pressure of sensitized dogs had been raised with barium chloride, the subsequent administration of a shocking dose of antigen failed to cause the drop in blood pressure characteristic of anaphylactic shock Even when treatment was not given until after shock, when the blood pressure had reached its lowest level, a rise of pressure could be obtained with barium chloride

Pfeiffer and Jarisch, in 1913, working with guinea pigs, found that barium chloride gave definite protection when injected intraperitoneally in doses from 0 005 to 0 05 gram, 30 minutes before the intraperitoneal injection of the shocking dose of antigen These experiments were well controlled They are not strictly comparable to those of other workers, who used lethal doses of antigen, as Pfeiffer and Jarisch gave doses of antigen small enough to allow a study of temperature changes in mild shock Other experiments in this same paper, however, are comparable, and showed that protection was obtained when 0 004 gram of barium chloride were given before the intravenous injection of the shocking dose of antigen In other experiments, barium chloride was added to the shocking dose of antigen, in the proportion of 8 7 cc of serum and 1 3 cc of a 10 per cent solution of the drug Two cubic centimeters of this mixture protected the 6 treated animals Four controls died

Summary The work of Biedl and Kraus cannot be evaluated on account of the lack of details The study of Pfeiffer and Jarisch offers valid evidence that anaphylactic shock can be inhibited with barium chloride, given either before or with the shocking dose of antigen

Barium sulphate

Lumiere and Couturier, in 1921 a showed that the intracardial injection of 0 5 cc of 0 265 per cent emulsion of barium sulphate, given just before the intracardial

injection of antigen, would protect guinea pigs against 1 minimum lethal dose of antigen Their hypothesis was that the drug saturated the precipitable elements of the blood, so that no further precipitation could occur upon the injection of antigen The experiments are conclusive in regard to the protection afforded, if not in regard to the explanation advanced

Barometric pressure reduction

Lumière and Couturier, in 1923, found that shock could be attenuated or repressed if guinea pigs, after the second injection of antigen, were placed under barometric pressure reduced from 30 to 40 cm of mercury In the first series 17 of the 20 controls died and 3 had acute shock, that is the mortality was 85 per cent Of the 25 animals kept under reduced pressure for 6 minutes, 8 died at once and 14 had moderately severe shock, 2 of these dying later Excluding these 2 animals, the authors considered this a mortality rate of 32 per cent In a second series of 160 animals, the mortality for the controls was over 80 per cent and for the treated animals under 40 per cent The details of these experiments were not given However, this was undoubtedly one of the largest and best controlled series of experiments done and it offers definite evidence that a reduction of barometric pressure can influence the degree of shock

Bayer 205 (Germanin)

Makarowa and Zeiss, in 1926, stated that anaphylactic shock could be prevented in serum-sensitized animals by the addition of 2 per cent of Bayer 205 to the shocking dose of serum We have been unable to find the protocols for this work

Schmidt, in 1926, from an uncontrolled study of 3 guinea pigs, concluded that 0 3 gram per kilogram of Bayer 205, given subcutaneously, could protect pigs from shock

Collier, in 1927, in experiments which included 1 control animal, decided that Bayer 205 given before or with the shocking dose of antigen prevented or inhibited shock in 50 per cent of the treated animals

Wiechmann and Koch, in 1928, criticized Collier's work and presented adequately controlled experiments to show that 0 2 gram of Bayer 205 afforded no protection when given 1 day after the first injection of antigen, 1 day or 1 hour before the shocking dose of antigen, or combined with the latter

Summary The only valid work on Bayer 205 is that of Wiechmann and Koch, which shows conclusively that, under the test conditions, the drug, given before or with the second dose of antigen, confers no protection against anaphylactic shock It would be of interest to carry out experiments with Bayer 205 similar to those of Swarez and Schaeffer with "arsenobenzene," that is, treating the shocking serum in vivo

Bayer 1910

The work of *Collier*, in 1927, is invalid for reasons discussed above

Benzoic acid

Amberg and Knox, in 1912, obtained no inhibition of cutaneous reactions in sensitized animals treated with this drug, as a control for experiments with sodium iodoxybenzoate

Benzol

Schiff, in 1915, studied benzol because of its selective action on the hematopoetic system and in relation to antibody formation Guinea pigs were treated with multiple small doses of benzol, 0 01 cc., intraperitoneally, both before and after sensitization There was a slight average increase in the number of white blood cells The treated animals were more sensitive than the controls An analysis of the protocols, however, shows that the series of treated animals and of controls were small, with several variations of shocking dosage of antigen, so that the differences observed might well have been within the limits of experimental variation But when the benzol dosage was increased to 0 03, which caused a drop in the white blood count, there was a clear cut difference in favor of the 11 treated animals, of which 9 lived Six of the 7 controls died The author believed that benzol did not cause an absence of shock, but rather a lowering of the sensitivity

Bile

Doerr, in 1908, cited the use of bile, but gave no reference

Blood volume increase

The inhibition of shock in pregnancy was considered due to an increase in blood volume by *Lumière and Couturier 1922* Bornstein also attributed the inhibitory action of sodium chloride to the same cause

Brain surgery

Friedberger and Gröber in 1913, noting the parallelism between anaphylaxis and poisoning with members of the morphine group found that the latter caused first a dilatation and then contraction of the brain tissue, with an irritation of the vagus center, resulting in the lung findings characteristic of morphine poisoning Believing that trephination should remove or at least reduce the action of such poison upon the nervous system, Gröber made experiments to test this point and found that such actually was the case The authors therefore, were interested in studying anaphylaxis in the same way After sensitization guinea pigs were trephined and the dura widely incised Of the 8 controls 7 died after shock with 0 23 to 0 35 of antigen per kilogram, the lungs showing characteristic changes, 1 control surviving 0 26 cc of antigen Of the 8 trephined animals, none died at once after shock and when death finally occurred the lungs were slightly or not at all distended The authors therefore concluded that in most cases animals would be protected against 2 or 3 minimum lethal doses of antigen, although death sometimes occurred within ¾ of an hour, even after only one fifth of a lethal dose

Schurer and Strassmann in 1912 extirpated the cerebrum of 6 sensitized guinea pigs While both controls died from 0 1 cc of antigen (horse serum) given intravenously, of the 5 treated pigs given 0 1 cc , 1 lived 48 hours, 2 lived 24 hours, 1 died soon, its lungs showing no distension and 1 died at once One animal given 0 2 cc of antigen also died at once The authors concluded that the brain extirpation did not confer protection

Butyric acid

Rosenau and Anderson, in 1906, obtained no inhibition of shock by treating 25 cc of the serum used for the second injection with 10 cc of N/10 butyric acid The mixture was kept for 40 hours at 15°C Three cubic centimeters of the filtrate killed 1 guinea pig Controls were killed with 6 cc intraperitoneally Since many controls were also killed by the intraperitoneal injection of 0 1 cc of serum, it is impossible to evaluate this one test

Caffein

Doerr, in 1908, cited the use of this drug, but without reference.

Calcium acetate

Anderson and Rosenau, in 1908, gave 0 1 mgm of this drug subcutaneously to 1 guinea pig 24 hours before shock with 0 5 cc of serum given in the brain No protection was obtained against what may have represented many lethal doses of antigen

Calcium chloride

Netter, in 1906, reported a carefully controlled clinical experiment upon the administration of calcium chloride to children who were given diphtheria antitoxin In the control group of 264 cases, including 258 which had no calcium chloride and 6 insufficiently treated cases, the number of cases of urticaria was 41, an incidence of 15 53 per 100 In the group of 252 cases given 1 gram a day of calcium chloride by mouth on the day of the serum injection and for 2 days thereafter, there were 6 cases of urticaria, an incidence of 2 38 per 100 This makes a difference in incidence between the controls and the treated cases of 13 15 per 100, which is statistically significant

In a later article, in 1926, *Netter* recommended that treatment be proportionate to the amount of serum given

Besredka, in 1907, made the general statement that calcium chloride prevented shock if given the night before the second injection of antigen

Rosenau and Anderson, in 1908, however, reported no inhibition of shock by giving calcium chloride in a dosage of 0 1 gram the day before shock Only 1 animal was used In Hygienic Laboratory Bulletin No 50, in 1909, these same authors reported no effects with from 0 1 to 0 15 gram of calcium chloride given subcutaneously to 3 guinea pigs 10 minutes after they had received intraperitoneally 6 cc of the shocking dose of antigen Other experiments reported in this

study, in which calcium chloride was given to counteract the effects of magnesium sulphate, were also unsuccessful

Biedl and Kraus, in 1909, made an unsupported statement that Netter's work was without value

Belin, in 1911, giving from 4 to 12 doses of 5 centigrams each by mouth for 2, 4 or 6 days before shock, in a total series of 3 guinea pigs, found that these 3 treated animals recovered after acute shock, while the 1 control died The antigen was injected into the brain No conclusions can be drawn from this experiment

Belin, in 1913, concluded that calcium chloride never inhibited shock when given with the antigen

Summary The clinical experiment of Netter seems to offer valid evidence of the value of calcium chloride, but the experiments of Besredka and of Belin, also favorable, do not present acceptable proof Rosenau and Anderson have presented definite evidence that, under their test conditions, the drug was without value when given either before or after the shocking dose of antigen The test conditions, however may have represented many lethal doses of antigen

Calcium lactate

Netter, in 1906, made a general statement that calcium lactate could be employed as well as calcium chloride to prevent serum sickness

Kastle, Healey and Buckner, in 1913, studied the effect of calcium lactate upon anaphylaxis in the guinea pig Unfortunately the results were inconclusive because of the insufficient controls, although the authors believed that good protection was obtained by treating female guinea pigs during the sensitization period

Summary There is no definite evidence that calcium lactate has any inhibitory effect upon anaphylactic shock

Calcium sulphate

See Perrin and Abel, 1927, under Mineral Waters

Cascosan

Rusznyák and Korányi, in 1927, studied this and other heteroproteins in guinea pigs sensitized with horse serum The method used was that of observing temperature changes Treatment with "Cascosan" and other proteins, caused a rise of temperature Subsequent injection of from 0 5 to 1 mgm of the specific antigen, given intraperitoneally, failed to cause the rise of temperature usual after the administration of such small amounts of antigen No protocols were given and only a few temperature charts Nevertheless, the work is of interest

Castration

See the article by *L umière and Couturier*, 1921 b under Pregnancy

Chloral hydrate

Benzhaf and Tamulener, in 1908, found that 75 per cent of their sensitized animals could be protected from shock if they were given chloral hydrate in doses

just sufficient to produce hypnosis The drug was given in a 10 per cent solution, 75 mgm or 100 mgm per gram of body weight Injections were made intramuscularly, 20 to 30 minutes before the intraperitoneal injection of 5 cc of horse serum, the shocking dose of antigen Upon recovery from the drug, from 1½ to 2½ hours later, the treated animals were free from symptoms

Banzhaf and Famulener, in 1910, obtained excellent results when the shocking dose of antigen was given intraperitoneally 20 or 30 minutes after the intramuscular injection of from 85 to 180 mgm of chloral hydrate Eleven of the untreated controls died and 12 of the 13 treated animals lived Similar treatment 20 to 30 minutes before shock was of no value, however, when the shocking dose of antigen was given intracardially When both drug and antigen were given intracardially, 8 out of 9 animals were protected by from 1 to 3 injections of drug from 2 to 4 minutes before injection of the antigen Multiple intracardial treatments 12 to 15 minutes before shock were of no value in 2 cases The experiments were well controlled and the paper is one of the best we have encountered

Rosenau and Anderson, in 1909, *or Anderson and Rosenau*, 1909, found that 200 mgm of chloral had no marked effect when given intramuscularly in a 5 per cent solution, either 2 hours or from 21 to 31 minutes before the intraperitoneal injection of the shocking dose of antigen, 6 cc of horse serum Three guinea pigs, given 250 mgm of chloral 30 minutes before the same amount of antigen recovered, after having shock symptoms Controls given for these tests are to be found in the authors' publications in 1906 From these it is found that 6 cc represents multiple lethal doses of antigen

Anderson and Schulz, in 1909, as previously cited under "adrenalin" obtained inhibition of shock by treating with a combination of chloral hydrate, urethane and adrenalin, also with artificial respiration with oxygen The exact rôle of the chloral hydrate in these tests could not be determined, because no experiments were done with that drug alone Careful drug toxicity controls were made

Summary Banzhaf and Famulener have offered satisfactory evidence that chloral hydrate may inhibit anaphylactic shock when given before the shocking dose of antigen and under certain conditions, not under others The negative results of Rosenau and Anderson are less valid on account of the lack of controls, as the shocking dose of antigen in their tests may have been too high

Chloralose

Besredka, in 1908, stated that 0 05 gram of this drug caused animals to live several hours after shock, the controls dying in 2 to 3 minutes

Chloroform

Rosenau and Anderson, in 1908, found that the addition of 0 4 per cent of chloroform to serum for preservative purposes had no inhibitory effect upon shock

Kopaczewski, *Roffo and Roffo*, in 1920, working on the theory that chloroform lowered the surface tension of the blood, tried to inhibit shock by giving chloroform

intravenously in water The injection of 1 5 cc of a 1 per cent solution of chloroform intravenously just before the intravenous injection of 0 5 cc of the shocking dose of antigen protected all of the animals so treated, all of the controls dying The number of animals used was not stated Nevertheless, the experiments were of interest

Summary The action of chloroform as an anesthetic has not been studied Its presence in the shocking dose of serum in the amount usually employed for purposes of preservation has been shown by Anderson and Rosenau not to inhibit shock with large amounts of antigen The intravenous administration of chloroform has been found by Kopaczewski, Roffo and Roffo to protect an unstated number of animals and this is the most valuable of the contributions on the use of chloroform in anaphylaxis

Cholesterin

Richard and Flandin, in 1911, made a general statement that results with cholesterin were less certain than with ovolecithin, but details were not given

Carpani, in 1920, injected cholesterin, 3 cc of a 5 per cent solution in olive oil and protected sensitized guinea pigs from shock The series was small but well controlled

Surányi and Jarno, in 1928, sensitized guinea pigs with 1 cc of horse serum, a very large amount in proportion to the amounts commonly used From 22 to 25 days later, some of the animals were given cholesterinized serum and others normal serum The shocking dose of antigen was given intracardially, the dosage not being stated Of the 10 controls, given normal serum, 9 died, and 1 had mild shock Of the 10 animals treated with cholesterinized serum, 1 died, 7 had bad shock with recovery and 2 had mild shock Controls of serum treated with acetone were not protected Giving animals daily feedings of 0 25 gram of cholesterin, mixed with their food, for about 24 days during the sensitization period had no effect

Summary The experiments of Surányi and Jarno were valid and showed that cholesterinized serum was less toxic than normal serum for the shocking dose While these findings are unquestionable for the conditions of the experiment, it is possible that on account of the large amount of antigen used for sensitization, the animals were less sensitive than those used in most of the experiments by others on inhibition of anaphylactic shock The work of Carpani, in which guinea pigs were injected with cholesterin in olive oil before shock, also showed definite protection

Cholin hydrochloride

Zunz and LaBarre, in 1923, found that 2 centigrams of choline hydrochloride, given intraperitoneally 15 to 25 minutes before the injection of a minimum lethal dose of antigen would protect a certain number of guinea pigs from death

Complement fixation

Loeffler, in 1910, exhausted complement in vivo by the intraperitoneal injection of a haemolytic system (3 cc of sheep red blood cells and 1 cc of anti-sheep serum) This was done 1 hour before the second dose of antigen No shock occurred if the necessary amount of treatment had been given The shocking dose of antigen was 5 cc , given intraperitoneally While both controls died, the 2 treated animals lived Although the series was small, the idea is of interest A control of the amount of complement present after treatment would have been of value

Congo red

Karsner and Ecker, in 1924, obtained no inhibition of shock with from 0 1 to 0 005 mgm per kilogram of this colloid, given in 1 or 0 5 per cent suspension either 1 or 24 hours before 2 lethal doses of antigen Of the 13 animals treated, 3 died from the drug, 6 of the 7 remaining died when given 2 lethal doses of antigen 1 hour after treatment Of 3 treated animals, given 2 lethal doses of antigen 24 hours after treatment, 2 died The number of controls was not given

Curarin

Auer and Lewis, in 1920, found that a "liberal dose" of curarin, i e 1 or 2 mgm , given intravenously, caused no inhibition of shock, artificial respiration being given after the drug

Dextrin

Karsner and Ecker, in 1924, treated sensitized guinea pigs with from 0 4 to 0 8 mgm per gram of this colloid Of the 12 treated animals, 2 died from the drug Of 6 treated animals given at an unstated time a dose of antigen lethal for 2 controls, 2 died and 4 recovered from shock Four treated animals given the same amount of shocking dose of antigen 24 hours after treatment all lived, 2 controls dying The authors, however, taking into consideration the variations in reaction obtained in the control series, did not consider this definite inhibition of shock, a conclusion most welcome after those of many other authors The description of these experiments with dextrin is not entirely clear

Dialysis of the antigen

For the negative results of Anderson and Rosenau, see Ammonium Sulphate

Diastase

Doerr, in 1908, cited the use of diastase, but without reference

Dichlorethylsulphid (mustard gas)

Corper, Black and Moore, in 1922, gave maximum non-lethal doses of mustard gas subcutaneously before or with the sensitizing injection of antigen, or during the

period of sensitization, without any effect upon the degree of shock This trial of mustard gas was based on previous experiments by Hektoen and Corper, in 1921, in which it had been shown that the gas, as a leucotoxic agent, exerted an inhibitory effect upon the production of antibodies

Drying of the antigen

See also Heating of the Antigen

Rosenau and Anderson, in 1906, found that drying horse serum did not destroy its toxic properties Only 1 animal was used and there may or may not have been a diminution of toxicity This method of modification is closely related to specific desensitization

Egg fat

See Antitrypsin, for the work of *Jobbling and Petersen* on egg fat

Emulsin

Doerr, in 1908, cited the use of emulsin, but without reference

Eserine (physostigmine)

Levy-Solal and Tzanck, in 1923, added this alkaloid to the shocking dose of antigen, given intracardially, without inhibiting shock The experiment was not of value, as about 2 animals were used, which were given the large amount of 1 cc of serum for shock

Ether

I Combined with the antigen *Besredka*, in 1907, obtained no inhibition of shock by extracting the serum antigen with ether

II Used as an anesthetic *Besredka*, in 1907, reported that if sensitized guinea pigs were anesthetized with ether before the second injection of antigen, 0 25 cc of horse serum, given in the brain, the animals had no shock, and upon recovery were desensitized No protocols were given In 1908, *Besredka* stated his belief that ether acted by making the nerve cells indifferent to the antigen antibody combination

Rosenau and Anderson, in 1908, produced anaphylactic death in 7 of the 8 guinea pigs etherized before the injection of the shocking dose of antigen This was 6 cc , given intraperitoneally, which according to the 1906 controls of these authors, represented many lethal doses

Banzhaf and Tamulener, in 1908, were likewise unable to inhibit shock with ether narcosis

Thomsen, in 1917, found only insignificant differences between the controls and treated guinea pigs which varied in weight from 340 to 400 grams The treated animals were deeply etherized before the intravenous injection of the shocking dose of serum In a second series, in which the animals weighed from 800 to 900 grams,

Complement fixation

Loeffler, in 1910, exhausted complement in vivo by the intraperitoneal injection of a haemolytic system (3 cc of sheep red blood cells and 1 cc of anti-sheep serum) This was done 1 hour before the second dose of antigen No shock occurred if the necessary amount of treatment had been given The shocking dose of antigen was 5 cc , given intraperitoneally While both controls died, the 2 treated animals lived Although the series was small, the idea is of interest A control of the amount of complement present after treatment would have been of value

Congo red

Karsner and Ecker, in 1924, obtained no inhibition of shock with from 0 1 to 0 005 mgm per kilogram of this colloid, given in 1 or 0 5 per cent suspension either 1 or 24 hours before 2 lethal doses of antigen Of the 13 animals treated, 3 died from the drug, 6 of the 7 remaining died when given 2 lethal doses of antigen 1 hour after treatment Of 3 treated animals, given 2 lethal doses of antigen 24 hours after treatment, 2 died The number of controls was not given

Curarin

Auer and Lewis, in 1920, found that a "liberal dose" of curarin, i e 1 or 2 mgm , given intravenously, caused no inhibition of shock, artificial respiration being given after the drug

Dextrin

Karsner and Ecker, in 1924, treated sensitized guinea pigs with from 0 4 to 0 8 mgm per gram of this colloid Of the 12 treated animals, 2 died from the drug Of 6 treated animals given at an unstated time a dose of antigen lethal for 2 controls, 2 died and 4 recovered from shock Four treated animals given the same amount of shocking dose of antigen 24 hours after treatment all lived, 2 controls dying The authors, however, taking into consideration the variations in reaction obtained in the control series, did not consider this definite inhibition of shock, a conclusion most welcome after those of many other authors The description of these experiments with dextrin is not entirely clear

Dialysis of the antigen

For the negative results of Anderson and Rosenau, see Ammonium Sulphate

Diastase

Doerr, in 1908, cited the use of diastase, but without reference

Dichlorethylsulphid (mustard gas)

Corper, Black and Moore, in 1922, gave maximum non-lethal doses of mustard gas subcutaneously before or with the sensitizing injection of antigen, or during the

period of sensitization, without any effect upon the degree of shock This trial of mustard gas was based on previous experiments by Hektoen and Corper, in 1921, in which it had been shown that the gas, as a leucotoxic agent, exerted an inhibitory effect upon the production of antibodies

Drying of the antigen

See also Heating of the Antigen

Rosenau and Anderson, in 1906, found that drying horse serum did not destroy its toxic properties Only 1 animal was used and there may or may not have been a diminution of toxicity This method of modification is closely related to specific desensitization

Egg fat

See Antitrypsin, for the work of *Jobbling and Petersen* on egg fat

Emulsin

Doerr, in 1908, cited the use of emulsin, but without reference

Eserine (physostigmine)

Levy Solal and Tzanck, in 1923, added this alkaloid to the shocking dose of antigen, given intracardially, without inhibiting shock The experiment was not of value, as about 2 animals were used, which were given the large amount of 1 cc of serum for shock

Ether

I Combined with the antigen *Besredka*, in 1907, obtained no inhibition of shock by extracting the serum antigen with ether

II Used as an anesthetic *Besredka*, in 1907, reported that if sensitized guinea pigs were anesthetized with ether before the second injection of antigen, 0 25 cc of horse serum, given in the brain, the animals had no shock, and upon recovery were desensitized No protocols were given In 1908, *Besredka* stated his belief that ether acted by making the nerve cells indifferent to the antigen antibody combination

Rosenau and Anderson, in 1908, produced anaphylactic death in 7 of the 8 guinea pigs etherized before the injection of the shocking dose of antigen This was 6 cc , given intraperitoneally, which according to the 1906 controls of these authors, represented many lethal doses

Banzhaf and Famulener, in 1908, were likewise unable to inhibit shock with ether narcosis

Thomsen, in 1917, found only insignificant differences between the controls and treated guinea pigs which varied in weight from 340 to 400 grams The treated animals were deeply etherized before the intravenous injection of the shocking dose of serum In a second series, in which the animals weighed from 800 to 900 grams,

there was a difference in favor of the anesthetized animals In a third series, of which no protocols were given, the weights of the animals being from 550 to 400 grams the results confirmed those of the second set However, if more highly sensitized animals were used, they were as little influenced by narcosis as the smaller animals of the first set The author believed that when shock was inhibited by ether narcosis, it was due to an interference with the antigen-antibody reaction, possibly by the action of the narcotic on the lipoids of the blood tissues Unfortunately so many different doses of antigen were given to shock in these tests, that not enough evidence was available to make any given test conclusive, as no allowance was made for the individual variations of the animals

III The intravenous injection of ether without narcosis Kopaczewski, Roffo and Roffo, in 1920, working on the theory that ether and other substances lowered the surface tension of serum, tried to repress shock by giving sensitized guinea pigs 2 5 cc of an aqueous solution of ether, saturated at 15°C The number of animals used was not given, but it was stated that all of the controls died upon the intravenous injection of 0 5 cc of the serum antigen, while the treated animals lived In view of these findings, the authors believed that the action of the nervous system in shock was of less importance than changes brought about by colloidal flocculation

Summary of experiments with ether Evidence that the ether extraction of serum antigen does not influence its ability to shock has been offered by Besredka, without protocols

Experiments, also without protocols, by Besredka, showing that deep ether narcosis inhibited shock, have not been confirmed by Rosenau and Anderson, or by Banzhaf and Famulener However, the shocking dose of antigen used by Rosenau and Anderson represented multiple lethal doses and Banzhaf and Famulener gave no protocols The experiments of Thomsen, in which there was some evidence of inhibition of shock under certain conditions, are not striking, because of the diversity of tests done with a small number of animals

The inhibition obtained by Kopaczewski, Roffo and Roffo by giving ether intravenously seems to be valid, but would be more conclusive if the number of animals used were known

It may be said that there is no absolutely final and conclusive demonstration that ether inhibits anaphylaxis, whether given with the shocking dose of antigen, or administered before shock as a narcotic or intravenously

Ethyl chloride

Besredka, in 1908, obtained good protection with this narcotic, but gave no details of his experiments

Filtration

Rosenau and Anderson, in 1906, found that filtration of horse serum through a Pasteur-Chamberland filter B did not destroy the antigen's toxic properties

Form aldehyde

Doerr, in 1908, also gave no details as to the use of formaldehyde

Freezing and thawing of the serum antigen

Besredka, in 1919, noted that freezing and thawing did not modify the toxicity of the antigen

Gastric juice

Lesné and Dreyfus, in 1911, obtained no inhibition of shock by adding porcine or canine gastric juice to the sensitizing or shocking dose of antigen, actinocongestin

Gelatin

Belin, in 1911, gave an unstated number of sensitized guinea pigs 20 per cent gelatin with the shocking dose of serum antigen without obtaining any protection

Gland extracts

For failure to inhibit shock by the administration of sexual gland extracts, please see Lumiere and Couturier, under Pregnancy See also Thyroid Extract

Glucose

Richet, Brodin and Saint-Girons, in 1919, found in dogs that diluting the shocking dose of serum to 9 times its volume with 1 or 4 5 per cent glucose caused no inhibition of shock The amount of antigen, however, may have been too high More experiments should be done with glucose

Glycogen

Karsner and Ecker, in 1924, gave 0 025 and 0 05 mgm per gram of glycogen to sensitized guinea pigs When treatment was given 45 minutes before shock, all of the 3 animals which had received the smaller dose of glycogen, as well as 3 of the 4 which had been given the larger dose, died in acute shock When treatment was given 24 hours before shock, all 3 of the animals given the smaller dosage of glycogen died, but 3 of the 4 given the larger dose lived The authors, however, believed that to conclude that there had been inhibition would be fallacious

Guanidine chloride

Heyde, in 1912, gave guanidine to guinea pigs sensitized with beef serum His reason for doing so was that guanidine, present in the urine of anaphylactic animals, itself produced shock No protocols were given Half of the controls died, but the treated animals had no shock when given antigen intraperitoneally 3 days later

Heating of the serum antigen

Rosenau and Anderson showed that heat modified the toxicity of serum, whether undiluted (1906), diluted (1908) or dried (1909)

Besredka, in 1919, summarized his experiments with diluted serum He both confirmed Rosenau and Anderson and showed that the toxicity of serum could be lowered by heating at 56° or 60°C on successive days

This work is obviously closely related to specific desensitization

Heparin

Keyes and Strauser, in 1926, found that while all of their 12 control pigeons had "multiple shock symptoms," 11 of the 12 birds treated with 1 cc of 1 per cent heparin 45 minutes before the second dose of antigen had no shock and the twelfth mild shock The work was well controlled and of value

Hyde, in 1927, found that all of his serum-sensitized control guinea pigs died when given 1 cc of antigen intravenously The animals given 7 mgm of heparin 45 minutes before shock also died Ten mgm of heparin given 5 minutes before shock failed to protect From these experiments he concluded that heparin did not inhibit fatal issue This conclusion in our opinion is not valid, because no titration of the antigen was given and the amount used, 1 cc , may have represented many lethal doses

Reed and Lamson, in 1927, obtained no inhibition of shock by giving 40 mgm of heparin intraperitoneally from 10 to 40 minutes before the intraperitoneal or intracardial injection of the shocking dose of antigen The sensitizing dose of antigen was high, from 2 to 5 cc of serum Of the 22 controls, 50 per cent died within 24 hours after shock, while of the 28 treated animals, 49 per cent died within the same period

Williams and van de Carr, in 1927, treated guinea pigs with heparin from 15 to 145 minutes before shock and found that of their 11 treated animals, only 1 had acute shock, while of the 8 controls, 2 lived and 6 died They concluded, with validity, as follows "The results obtained appear to indicate that the injection of heparin into the circulation in amounts sufficient to prevent the formation of a blood clot prevents or reduces, in the majority of cases, the symptoms of anaphylactic shock in guinea pigs hypersensitive to horse serum "

In 1928, *van de Carr, Lyons and Williams*, in a careful study, found that "heparin, even when given in amounts sufficient to render the blood incoagulable for 72 hours will not prevent or alleviate the anaphylactic syndrome in guinea pigs when the colloidal balance of the blood has been disturbed by the previous injection of heterophile antigen "

Hanzlik, Butt and Stockton, in 1928, studying the reciprocal action of the crop muscles of pigeons in anaphylactic shock got no protection with heparin given 45 to 90 minutes before the second dose of antigen The amounts of heparin and antigen used were not given

Summary The experiments of Keyes and Strauser and of Williams and van de Carr showing inhibition of anaphylactic shock with heparin were carefully controlled and valid The work of Hyde, with negative results, is less valuable because there was no titration of the shocking dose of antigen The negative ex-

periments of Reed and Lamson were well controlled, but the sensitizing dose of antigen had been high and most of their animals were shocked intraperitoneally The in vitro studies of Hanzlik, Butt and Stockton are not strictly comparable to the in vivo work More sound evidence in favor of some protection under certain circumstances is available, therefore, than is negative evidence under other conditions

Heterophile antigen

Van de Carr, Lyons and Williams, in 1928, found that heterophile antigen, given intravenously to guinea pigs previously sensitized with casein, so altered the colloidal state of the blood as to increase the toxicity of the second injection of antigen The neutralization of the inhibitory action of heparin by an injection of heterophile antigen has been cited under Heparin

Hirudin

Friedberger, in 1910, stated that inhibition of blood coagulability by hirudin was without influence, even against a small multiple of the minimum lethal dose of antigen Two controls were used Seven animals given hirudin at different times before shock all died The amount of the shocking dose of antigen was calculated per 100 grams of body weight A general statement was made that hirudin had no effect if given 24 hours before the antigen

Zunz and van Geertruyden Bernard, in 1921, found that the minimum lethal dose of antigen was increased if the serum had been treated from 3 to 4 hours before injection with 2 mgm of hirudin per 7 cc of serum If from 2 to 4 mgm of hirudin was given intravenously to sensitized animals from 2½ to 4 hours before shock, protection was obtained, but not against many lethal doses of antigen No details of these experiments were given

Summary There is no conclusive evidence that hirudin inhibits shock, the negative results of Friedberger were fully as conclusive as the evidence of Zunz and Van Geertruyden Bernard that some protection was obtained

Hydrochloric acid

Lesné and Dreyfus, in 1911, obtained no inhibition of shock by adding 0 33 per cent of this acid to the sensitizing or to the shocking dose of the antigen, actinocongestin

Hydrogen peroxide

Rosenau and Anderson, in 1906, added 5 cc of this drug to 25 cc of serum The mixture was kept at 15°C for 40 hours and then filtered Three or 6 cc of the filtrate was injected into the peritoneal cavities of 2 sensitized guinea pigs respectively and both recovered In 1906, these authors demonstrated that 0 1 cc of horse serum would kill sensitized animals If the amounts of treated and untreated serum were comparable, these 2 animals had been protected against many lethal doses of antigen

Ink (China)

Michelazzi, in 1920, treated 4 sensitized guinea pigs with 2 cc of 20 per cent China ink 48 hours before shock Two of the animals died that were given more than the minimum lethal dose of antigen Two survived, 1 of these had had slightly more than the lethal dose and 1 less The controls were given a larger sensitizing dose of antigen and therefore were not comparable

Moldovan and Zolog, in 1923, used 0 25 cc of China ink per 100 grams of body weight, the ink being diluted with equal parts of water They found that no protection was obtained when the ink was given intravenously either 8 minutes or 15 days before the minimum lethal dose of antigen If the ink was given from 1 hour to 10 days before the shocking dose of antigen, animals were protected against from 2 5 to 4 minimum lethal doses, larger amounts of antigen killing No protocols of the experiments were given

Moldovan and Zolog, in 1923, in an article following the one just cited, explained the protective action of China ink as due to the fact that after the deposition of carbon in the endothelial cells of the liver, a substance was secreted which prevented bronchial spasm and which was antagonistic to the active principle of anaphylaxis Pituitrin given between ink injection and shock removed protection No protocols are given to confirm this generality

Moldovan and Zolog, in a third paper (1925), performed some original experiments which would be of value if confirmed by a larger series Rabbits were injected intravenously with 5 cc of 1 per cent China ink diluted with equal parts of water and were bled to obtain serum 2, 7 and 12 days thereafter These sera were given to guinea pigs sensitized with normal horse serum 5 minutes before shock and seemed to protect them from multiple lethal doses of the antigen All of the untreated controls, the number not being stated, died from smaller doses of antigen, as well as the 1 animal treated with normal rabbit serum Unfortunately, only 1 animal was reported for each of the treated sera Similar experiments with guinea pig serum obtained 2 days after ink injection protected one sensitized guinea pig The serum from a guinea pig bled 12 days after an ink injection and that of an untreated animal failed to protect one guinea pig apiece From these experiments, the authors concluded that a desensitizing principle was secreted in the blood after an injection of China ink It does not seem to us that it is necessary to advance such an explanation since the changes could conceivably be explained on some other basis Nevertheless, the work is of great interest and should be confirmed by larger series

Simitch, in 1926, was unable to protect animals by 4 intravenous injections of 1 cc of 3 per cent China ink, 1 day before the shocking dose of antigen The number of animals in the control and treated series was not given, but all died It is possible that the amount of antigen used for shock was too high

Simitch also failed to obtain any protection by giving ink 1 week after splenectomy and 1 day before the *sensitizing* dose of antigen

Summary There is no conclusive evidence that anaphylactic shock can be

inhibited by the injection of ink given before or during sensitization The small number of animals used in the experiments makes it impossible to evaluate the results The work of Moldovan and Zolog, especially their third paper, however, offers an interesting approach which seems worthy of more complete investigation

Intercurrent infection

This most interesting aspect of the problem has been approached by comparatively few workers, although more study along this line would be of value

Von Pirquet, in 1908, noted that tuberculous children lost their reactivity to tuberculin for about a week during measles

Hartoch and Sirenskij, in 1912, found that sensitized guinea pigs, infected with trypanosomes, became insensitive to lethal amounts of antigen This was explained by the authors on the basis of loss of complement, due to the intercurrent infection No protocols of antigen titration were given Of the 5 animals infected with Nagana trypanosomes 12 days after the sensitizing dose of antigen, and given the second injection of antigen 47 or 48 days after the first, 2 died of anaphylactic shock and 3 of infection The results, therefore, were suggestive, but inconclusive

Seligmann, in 1912, reported that guinea pigs infected with tuberculosis at the time of their sensitization with papain, resisted 5, 10 or 20 shocking doses of antigen lethal for the uninfected controls when shocked 4 or 5 weeks later This resistance was not, however, invariable, some of the infected animals dying subacutely from ½ to 2 hours after the shock The animals with localized tuberculosis died more quickly when fatally shocked, but required from 3 to 5 lethal doses The more generalized the tuberculosis, the more difficult was it to induce shock, 20 minimum lethal doses of antigen being necessary to kill some of these animals In animals infected before or after the time of sensitization, there ensued, with the appearance of the tuberculosis, a retrogression of sensitivity, similar to that in the animals infected at the time of sensitization No protocols were given for this set of experiments In a confirmatory series, the animals infected with tuberculosis after sensitization with papain were found to resist 3 minimum lethal doses of antigen 31 days later Some of the infected animals and uninfected controls were bled and their sera used to sensitize normal animals passively Twenty four hours later, when all of these animals received 1 cc of the antigen, the 2 sensitized with the blood of infected animals had no shock, while the 2 controls both had shock, fatal in 1 case Seligmann, therefore, concluded that the lessening of sensitivity in infected guinea pigs depended on the reduction of specific antibody, not on a lack of complement He also concluded that tuberculous infection in sensitized animals leads to a far spread loss of anaphylactic sensitivity

Friedberger, in 1913, performed experiments similar to those of Seligmann, except that he worked with mild shock in which temperature changes could be noted The work was carefully controlled and showed that, in general, much more

marked temperature changes occurred in the uninfected sensitized controls upon the second injection of antigen, than in the animals which had been infected with tuberculosis at the time of sensitization The lethal dose of shocking antigen was also found in most cases to be much higher for the infected animals than for the uninfected

Isaacs, in 1924, made an unsupported statement that acute distemper prevented desensitization, but that this infection in the recovery stage did not

Wedgewood and Grant, in 1924, observed that young rats on a complete diet could be sensitized if they had an infectious disease of the lungs, although normally such animals are resistant to sensitization The possible theory to explain this increased sensibility was that the infection exhausted the vitamin B reserves, which ordinarily protected against anaphylaxis

Lewis and Loomis, in 1926, concluded that the allergic irritability of guinea pigs was *increased* by infection with Brucella abortus or with a streptococcus, or by the injection of dead tubercle bacilli, all of these being less effective than infection with tubercle bacilli These experiments are not comparable to the others because of differences in technique

Summary The studies of Hartoch and Sirenskij, of Seligmann and of Friedberger have indicated a decreased susceptibility to shock in animals given an intercurrent infection On the other hand, Wedgewood and Grant, as well as Lewis and Loomis, using different methods of approach, have offered evidence of an increased irritability Certainly more work on this problem is clearly indicated

Invertin

Doerr, in 1908, cited the use of this without details

Iodbenzoic Acid

Ambert and Knox, in 1912, obtained no inhibition of the cutaneous reaction in sensitized guinea pigs treated with this drug before the second injection of antigen This drug was used as a control for experiments with sodium iodoxybenzoate

Iodine

Besredka, in 1907, was unable to modify the toxicity of serum with Gram's solution

Anderson and Rosenau, in 1908, found that the addition of 1 5 gram of iodine and 3 grams of potassium iodide to 25 cc of serum had no effect upon its toxicity Of 5 controls, given 6 cc of normal serum subcutaneously, 2 died and 3 recovered after acute shock Of 12 animals given the treated serum subcutaneously, 4 died, 1 recovered from severe shock and 7 had mild or slight shock. All 3 of the animals died that were given 6 cc of treated serum intraperitoneally When iodine was injected subcutaneously 1 or 24 hours before the intracranial injection of the

antigen, all of three animals so treated died Two of the 3 animals so treated 1 hour before the intraperitoneal administration of the antigen died The third recovered after marked symptoms Controls were given here only for the subcutaneous injection of the antigen Earlier controls, however, had shown that 6 cc of serum, given intraperitoneally, probably represented many lethal doses

Von Dungern and Hirschfeld, in 1911, concluded that the action of anaphylactic antibodies was strongly raised by iodinization Three guinea pigs, passively sensitized with untreated anti sheep serum all died when given sheep serum 24 hours later, while the 3 animals given iodinized anti sheep serum had mild or no shock upon the subsequent injection of antigen Experiments with active sensitization showed that after sensitization with normal horse serum, animals shocked with freshly iodinized serum reacted less violently than those shocked with normal serum or old iodinized serum Unfortunately, the small number of animals used for each variation of test makes the evaluation of these findings difficult Probably these findings should be interpreted as the result of a chemical change of the antigen

Summary There is some, but inclusive evidence, offered by von Dungern and Hirschfeld, that iodinization of the serum antigen may inhibit active or passive anaphylaxis Their findings are more complete than the earlier, negative work of Besredka and of Anderson and Rosenau

Iron in state of hydrosol

Henrijean and Kopaczewski in 1925, gave no details of their experiments with iron in this state

Iron oxide

Smitch, in 1926, failed to inhibit shock by giving a total of 4 cc of 6 per cent oxide of iron intravenously the day before sensitization Iron was used alone or 1 week after splenectomy No titration of the lethal dose of antigen was made No protocols were given and the number of animals used was not stated

Iron oxide, saccharated

Petersen, Jaffe, Levinson and Hughes, in 1923, gave dogs daily intravenous injections of 15 cc of 20 per cent saccharated red oxide of iron during the sensitization period The conclusion reached was that shock was modified by blocking the reticulo endothelial system in this way The authors believed that the so-called reticulo-endothelial blockade did not necessarily mean a diminished permeability of the endothelium, but that there might be either a true blockade of the cells or an increased activity of the endothelial elements, with a more rapid destruction of the antigen and a consequent protection of the parenchymal cells of the splanchnic area

Michelazzi, in 1927, found that the minimum lethal dose of antigen for 11 controls was 0 025 cc of serum per 300 grams of body weight Seventeen ani-

mals were given 4 subcutaneous injections of a 2 per cent solution of saccharated iron oxide on the fifth, fourth, third and first days before the sensitizing dose of antigen The minimum lethal dose of antigen for these animals was 0 05 cc of serum per 300 grams of body weight, or twice that of the controls Six animals were given 4 subcutaneous injections of 1 cc of saccharated iron oxide on 4 consecutive days, starting 24 hours after the first injection of antigen The minimum lethal dose of antigen for these animals was 0 3 cc of serum per 300 grams of body weight or 12 times that of the controls In another series, the minimum lethal dose of antigen for the 7 controls was 0 3 cc of serum per 100 grams of weight In the series of 7 animals treated with 4 cc of drug 4 hours before shock, the minimum lethal dose of antigen was 0 9 cc per 300 grams of weight, or 3 times that of the controls

Summary Michelazzi offered well controlled evidence that the administration of saccharated iron oxide modified shock if given before sensitization or during the sensitization period Similar results were obtained by Petersen, Jaffe, Levinson and Hughes by treating dogs during the sensitization period

Kephalin

Karsner and Ecker, in 1924, obtained some evidence of inhibition of shock with kephalin, given in dosages of 0 014 or 0 028 mgm per gram half an hour before shock In this series 3 of the 5 animals given the smaller dosage and all of the 5 given the larger dosage survived the shocking dose of antigen lethal for an unstated number of controls Results were less striking when treatment was given 1 hour before shock No protection was obtained when treatment was given 24 hours before shock Although extremely conservative in their conclusions and realizing the possible fallaciousness of their results, on account of the small number of animals, the authors concluded that their results with this colloid were sufficiently encouraging to justify further experimentation

Lanolin

Fujioka, in 1925, stated that both active and passive anaphylaxis could be prevented by blocking the reticulo-endothelial cells with an emulsion of lanolin We have been able to read only the abstract of this paper

Lecithin

Anderson and Frost, in 1910, gave 6 sensitized guinea pigs 0 25 gram of egg lecithin 24 hours before the injection of 5 cc of horse serum Five animals had shock, 1 of them dying The authors did not consider this indicative of any modification of shock

Banzhaf and Steinhardt, in 1910, obtained no protection by emulsifying lecithin with the shocking dose of antigen Lecithin given in doses of from 250 to 500 mgm , however, protected sensitized guinea pigs from 5 cc of horse serum given 20 hours later No protocols were given for these experiments

Achard and Flandin, in 1911, found that animals could be protected against shock by giving 0 25 gram of lecithin 2 hours before shock to 11 guinea pigs, or 0 1 gram the day before shock, given to 4 animals The injection of lecithin 30 minutes before shock attenuated it in 2 cases, but did not modify it in 2 others An unstated number of controls were shocked Details were lacking

Doerr, in 1913, cited previous experiments with both purified and egg lecithin with which he was unable to obtain any protection against anaphylactic shock

Carpani, in 1920, in a well controlled experiment with a rather small number of animals, injected lecithin subcutaneously, 3 cc of a 5 per cent solution in olive oil Protection against shock was obtained when this treatment was given before the second injection of antigen

Schneider, in 1927, obtained no inhibition of shock by treating animals with both radiation and subcutaneous injections of lecithin His series was very small

Summary There is no striking evidence that lecithin can inhibit shock The favorable reports of Banzhaf and Steinhardt, of Achard and Flandin and of Carpani are weakened either by a lack of details or by the use of too small a series of animals The same criticism applies to the unfavorable work of Anderson and Frost, of Doerr and of Schneider

Lipoids

For the work done with antitrypsin, kephalin and lecithin, the reader is referred to these headings

Duprez, in 1922, concluded that lipoids exerted an anti anaphylactic action He used the acetone insoluble Wassermann antigen of Bordet Guinea pigs sensitized with 2 cc of horse serum were given 2 cc of the lipoid emulsion intravenously 1 hour before shock The treated animals had very mild or no shock and an unstated number of controls died No protocols were given

Stern and Reiss, in 1922, working with dogs, found, as previously shown, that while the sensitizing injection of antigen caused an increase in the blood lipoids, in anaphylactic shock they were lowered within ten minutes after the injection of antigen The authors correlated the lipoid content of the blood with its non-coagulability in shock

Magnesium sulphate

Anderson and Rosenau, in 1908, found that no protection could be obtained by giving 0 1 gram of this drug subcutaneously the day before shocking by the injection of 0 5 cc of serum in the brain One pig was used This was the titrated minimum lethal dose

Rosenau and Anderson, in 1909, studied the effect of magnesium sulphate given subcutaneously as an anesthetic to sensitized guinea pigs before shock No inhibition of shock was obtained, whether calcium chloride was used to counteract the effect of the magnesium sulphate or not Thirty seven animals were

treated with different combinations, the amounts of serum for shock invariably being 6 cc given intraperitoneally Probably this represented multiple lethal doses

Summary There is no evidence that magnesium sulphate influences anaphylactic shock, but not all of the possibilities have been studied

Manganese chloride

Pico, in 1924, gave 35 guinea pigs 0 5 cc of manganese chloride in 0 4 per cent solution, just before the shocking dose of 1 cc of antigen Twelve of these treated animals had mild or no shock and 23 died No controls were given Nevertheless, the author stated that the animals had been almost completely protected It must however, have been difficult to determine the degree of protection in the 23 casualties Other experiments, done with sub-sensitizing injections of antigen and with manganese chloride treatment during the incubation period, were too small in number, although somewhat controlled, to allow any conclusions to be drawn The method, however, is of possible interest

Klopstock, in 1925, in a small, but controlled series, found that none of the 6 guinea pigs treated with 1 mgm of manganese chloride died when given the second injection of antigen, although 4 of them had severe shock Four of the 6 untreated controls died and 1 of the survivors had acute shock The author concluded that manganese chloride protected, but, in our opinion, the series was too small to be more than suggestive

Summary Of the 2 articles on the use of manganese chloride, Pico's is uncontrolled and his conclusions do not follow from the data presented Klopstock's well controlled work presented evidence in a small series of animals that the drug may have an inhibitory action There is, however, no entirely conclusive evidence in regard to manganese chloride

Mercurochrome–220

Martin and Hill, in 1930, found that while mercurochrome given intravenously in doses of 5 mgm per kilogram had no inhibitory action if given early in the sensitization period, when the drug was given the day before the shocking dose of antigen, the treated animals had definitely less shock than the controls Thus of 51 treated animals, 30, or 58 8 per cent lived and 21 died, while of the 37 controls, 13 or 35 1 per cent lived and 24 died

Mineral water

Billard, in 1913, sensitized guinea pigs with an unknown amount of antigen and gave one set 6 daily intraperitoneal injections of 2 cc of Eau de César A similar set received 2 cc of Eau de Saint-Mart (Royat) Fourteen days after sensitization, the shocking dose of antigen was given The sole survivors were the 6 animals treated with Eau de Saint-Mart The degree of the second injection was not given No distilled water controls were made

Chaussevant, Galup and Poirot Delpech, in 1913, studied transported Vichy water 24 hours old and found no difference between the treated guinea pigs and the controls which had received distilled water The authors believed, for no stated reason, that if mineral waters desensitized, it was on account of radio active substances contained therein

Gobert, in 1913, treated guinea pigs with 2 cc of water from Aïn Sbia (Korbous) for 11 days He agreed that Chassevant, Galup and Poirot-Delpech that the treated animals, when shocked, behaved like the controls The series was short but the number of controls, 4, equaled the number treated However, 3 different shocking doses of antigen were given these 8 animals

Billard and Grellety, in 1913, studying Vichy water, obtained results similar to those of Billard with Royat water They used rabbits, sensitized with horse serum, and found that while the animals treated with water from 1 spring Chanel, had almost no shock, those treated from 2 other springs had as much shock as the controls They therefore concluded that mineral waters could modify anaphylaxis favorably or unfavorably, depending upon the source of the water No protocols were given

Billard and Daupeyroux, in 1913, made a brief report of a study of Bourboule water at its source Twenty five rabbits were used, 5 controls and 5 in each group given different amounts of treatment The second dose of antigen was given on 3 different days after sensitization, so that the number of animals used for any given test must have been very small No protocols were given and it is difficult to evaluate the results, but the authors believed that definite attenuation of shock was obtained in some of the tests

Mougeout, in *1919*, worked with rabbits, continuing Billard's work He claims to have obtained good results

Ferreyrolles, in 1919, confirmed the findings of Richet, of Bellin, whom he cites without reference and of Daupeyroux Ferreyrolles, however, presented none of his own experiments

Galup, in 1920, summarized the articles to date, without giving further experimental work

Kopaczewski and A H Roffo, in 1920, reported experiments in which the 4 animals treated with mineral water had no shock, while the one and only control died It is impossible to draw definite conclusions from such a series On the theory that the sensitizing action of mineral waters was due to the presence of carbonates and bicarbonates, the authors also reported some experiments with these substances, which will be cited under the headings of Sodium Carbonate and Sodium Bicarbonate

Arloing and Vaulky, in 1921, studied transported Vichy waters hermetically sealed when collected and used 24 hours later Two controls were used, both of which had extreme shock, 1 dying in 24 hours and the other after 4 days Of 9 animals treated with mineral waters, 6 had mild or no shock and 3 died The authors concluded that both Vichy waters tested could attenuate or suppress

shock if given in sufficiently large amounts over a long enough time They also believed that the viscosity of the blood was augmented by these waters

Arloing and Vauthy, in 1922, in their second paper, gave daily subcutaneous injections of a 4 cc of various Vichy waters for 21 days The shocking dose of antigen was "quelques gouttes," given intracranially 24 hours after the last treatment The treated animals, 6 from each of 4 springs, had slight or no shock, while the four controls, 1 for each set, had severe shock, 3 with recovery This is certainly a suggestive paper

Arloing and Vauthy, in 1922, in a third paper, gave Vichy waters with the shocking dose of antigen, which was 0 25 cc of serum, diluted with either 0 75 or 4 75 cc of water The authors believed that they obtained definite protective action from all three sources The treated series was very small Of 4 treated animals, from each of 3 springs, all lived, while 1 of the 2 controls died This was not a striking paper, because only 1 animal was used for each variation of the experiment

Arloing and Vauthy, in 1923, in a fourth paper, mixed Vichy water with the sensitizing dose of antigen Five treated animals recovered with slight shock and 5 of the 6 controls died, the other being acutely shocked In this case, it is possible that the antigen, mixed with the mineral water, assumed another chemical structure and that the second injection of untreated antigenic serum therefore was not specific

Arloing, Langeron, Milhaud and Ricard in 1923, used sulphur water from Luchon They claimed that protection was obtained if the guinea pigs had 10 daily subcutaneous treatments with 2 cc of the transported water or 6 cc daily for 21 days They gave no controls There was no titration for the minimum lethal dose of antigen Various antigens were used and very few animals were treated The results cannot be accepted as authoritative

Cahn, in 1924, repeated the work of the French authors and was able to protect his guinea pigs with Vichy water The three treated animals that received from 16 to 19 daily injections of Vichy water lived after the shocking dose of antigen lethal for the controls Using German mineral water from Fachinger, Wildung and Emser, he obtained the same results with Emser water, but no results of any value with Fachinger or Wildung water Although this experiment was carried out with a small number of animals, the difference between the treated and control animals was marked

Henrijean and Kopaczewski, in 1925, studied the iron water of Spa and also iron in a state of hydrosol In the first set, all of the controls died, while all of the six guinea pigs treated with about 10 subcutaneous injections of 0 5 cc of the mineral water every 2 days for 20 days had very mild shock Of the animals treated in this way intraperitoneally, 50 per cent died and 50 per cent had mild shock Other experiments gave similar results with intraperitoneal treatment When treatment consisted of 1 injection of 2 cc of the mineral water injected intravenously just before the shocking dose of antigen, all died in 1 set and all had

moderate shock in another It is not clear that additional controls were made with the sets done after the first series as further controls were not recorded It is not valid to carry over controls from one set to others done at different times, so that the value of the other sets may be questioned The first set, however, was entirely valid

No details were given of experiments with iron in the state of hydrosol The authors concluded that distinct phylactic properties were possessed by the water studied In spite of their hypothesis that the water acts by augmenting the viscosity of the blood, i e , in stabilizing the humoral colloids, the authors finally concluded wisely, that the mechanism of desensitization is still to be explained

Perrin and Abel, in 1927, in an uncontrolled investigation, compared the desensitizing action of a mineral water containing calcium sulphate and equivalent solutions of calcium sulphate

Salvagnini, in 1927, obtained inconclusive results by treating guinea pigs with water from the hot springs of Abano With rabbits, however, he obtained some inhibition of shock Treating guinea pigs with mud from the same region intensified shock His experiments were carefully controlled and seem valid His bibliography contained a few references which we have been unable to obtain

Summary It is interesting to review the results critically We find 14 articles reporting upon the helpful effect of continuous injections of certain spring waters in allaying the fatal effects of the shocking dose of antigen

Actually, 5 of them offer some definite evidence The first is Billard, who, unfortunately, does not give satisfactory protocols The work of Arloing and Vauthy in 1922 seems valid The investigations of Henrijean and Kopaczewski, of Cahn and of Salvagnini were well controlled

For various reasons, the other six do not fulfill the very definite requirements of validity

In regard to negative results, the work of Chassevant, Galup and Poirot-Delpech was well done and they were unable to find any protection with transported waters

Milk

See also Whey Protein

For the technique of the experiments of *Rusznyák and Korányi*, in 1927, by which some inhibition of shock was obtained by injection of milk, please see "Cascosan"

In 1930, *Martin and Hill* found that the intramuscular injections of milk protein, (Aolan) throughout the sensitization period protected a certain number of guinea pigs from shock

Morphine

Besredka, in 1907, found that from 14 to 18 centigrams of morphine hydrochloride caused no true narcosis in sensitized guinea pigs and that when shocked, the treated animals died in the same manner as the controls

Banzhaf and Famulener, in 1908, made a general statement that they could obtain no inhibition of anaphylactic shock with morphine sulphate

Summary There is no evidence from the studies of Besredka or Banzhaf and Famulener that morphine has any inhibitory action

Multiple sensitization

Most of the early work done with multiple antigens was marred by the large amounts of antigen given in both the sensitizing and the shocking doses and also because most of the injections were made intraperitoneally

However, the work of *Gay and Southard*, in 1908 is decidedly worthy of consideration They showed that when guinea pigs were sensitized with three antigens, non-lethal reinjection of 1 or 2 of these antigens was apt to desensitize the animal against the third This phenomenon varied according to the order in which the antigens, egg white, milk and horse serum, were given

Bessau, in 1911, carried out an experiment which has been more or less repeated by other investigators The main differences were that Bessau mentions only 1 control and later writers used a few Bessau, however, used a large dose of shocking antigen (0 5 cc), given intravenously, which should have been well over the minimum lethal dose He sensitized his animals with 2 sera and desensitized with small amounts of 1 of them, 0 05 cc given intravenously, or 1 or 2 cc given intraperitoneally Three of the doubly sensitized animals, which received 0 05 cc of one serum intravenously 5 hours before the shocking dose of the second antigen, all had shock but recovered, only 1 of these animals having a severe reaction None of the 8 doubly-sensitized animals lived that received the intravenous injection of 1 serum from 1 to 2 days before the shocking dose of the second serum Of 4 animals which received the desensitizing serum intraperitoneally 1 day before the shocking dose, and 1 each treated 2 and 5 days before shock, all recovered His small number of animals and the paucity of his controls, render Bessau's report of very little value in itself

Benjamin and Witzinger, in 1911, found that of 10 guinea pigs given 1 cc of horse serum 24 hours before sensitization with 0 01 cc of beef serum, 1 died when shocked with 0 2 cc of beef serum 9 days later, 3 had severe shock with recovery and 6 mild or no shock All 7 of the comparable controls for this series died The authors concluded that anaphylaxis could be inhibited by the injection of serum before sensitization Within the limit of the number of animals used, this conclusion seems justified This work should be compared with that of Weil, in 1914, on the inhibition of passive anaphylaxis by the injection of large amounts of normal serum before the administration of immune serum Weil's study is cited under Normal Serum

Bauer, in 1912, sensitized guinea pigs with beef serum and hog plasma He gave 4 of them 3 cc of beef serum intraperitoneally 2 days before shocking them with different amounts of hog plasma, given intravenously Two of these animals died, 1 having received 1 cc of hog plasma, an amount lethal for a normal

animal, and 2 had mild or no shock from doses of antigen lethal for the controls Although carefully controlled, the number of animals used for the experimental variations was too small to allow valid conclusions to be drawn

Szymanowski, in 1912, repeated in a more detailed manner the work outlined above He sensitized his animals with 2 antigens and then tried to desensitize with large, sublethal doses of one of them He was unable to show that the desensitization produced by the first antigen conferred more than a slight resistance to the second His work was well done, but may be criticized in that not enough animals received the shocking dose of the second antigen to make his estimation of the minimum lethal dose accurate

Kumagai and Odaira, in 1912, carried out parallel experiments with passive anaphylaxis When guinea pigs were sensitized with both anti sheep and anti human rabbit sera and shocked with 1 antigen and then with the other, the maximum non lethal dose of the first antigen was found not to protect against the second Only a few animals were used

Wells and Osborne, in 1913, found that heterologous proteins failed to give complete protection against the antigen, although animals sensitized with 2 antigens and shocked with one were less sensitive to the second

Weil and Coca, in 1913, found that after double sensitization, desensitization with 1 antigen rendered the animal only slightly more resistant to the second antigen

Dale, in 1912–13, came to the conclusion that when animals were sensitized with 2 or more antigens, "desensitization of the muscle with one antigen is not without effect on its sensitiveness to others" This work was done in vitro

Besson, Opitz and Preusse, in 1914, sensitized guinea pigs with 2 sera and then determined the lethal shocking doses of both Of five sensitized animals given sublethal amounts of 1 antigen, beef serum, and then given horse serum, the second antigen, 3 died and 2 lived, but the amounts of the second antigen given were too small to make any demonstration of inhibition of shock conclusive Experiments were also done with local anaphylaxis in rabbits It was concluded that in doubly sensitized rabbits the intravenous reinjection of only 1 serum influenced the appearance of local anaphylaxis with either the homologous or the heterologous antigen It is unfortunate that the number of animals used in some of this rather original work was not greater

J H Lewis, in 1915, demonstrated that the injection of large amounts of 1 type of animal serum or egg white before the serum which was to be used for antigen would definitely protect animals against the intoxicating dose of antigen This confirmed the earlier work of Benjamin and Witzinger, cited above Lewis had a rather small number of controls, but his work was carefully done and as accurate as it was interesting

Massini, in 1918, sensitized guinea pigs with 2 or 3 sera and found that a non-specific antianaphylaxis accompanied the specific desensitization His technique made use of excised tissue

Lumière and Couturier, in 1912, sensitized animals with 2 antigens and after 2 weeks administered subcutaneously sublethal doses of 1 of them Six and 4 hours later, the second antigen was given intracardially The controls died and the treated animals lived The next day the latter received 0 5 cc of the second antigen and died The experiment was well done and demonstrated desensitization lasting but a short time

Brack, in 1921, sensitized guinea pigs with 3 sera He found that their reaction was strongest to the antigen first used for sensitization and there was a clearly quantitative difference between specific and non-specific antianaphylaxis He used Massini's technique of studying excised intestinal muscle

Summary The work of Wells and Osborne, of Lumière and Couturier, of P Lewis and of Benjamin & Witzinger is all of value and seems to show that when 2 or more antigens are given simultaneously for sensitization, the subsequent injection of 1 of these antigens will decrease the sensitivity of the animals for the other antigen Dale, Massini and Brack, by their in vitro work, came to the same conclusion On the other hand, the well controlled work of Szymonowski, of Kumagai and Odaira and of Weil and Coco, did not produce evidence which could be so interpreted The work of Bessau and his associates is, unfortunately, not acceptable on account of the lack of controls

Myrosin

Doerr, in 1908, cited the use of myrosin, but gave no reference or description of the experiments

Neoarsphenamine

Jungeblutt, in 1928, studied the inhibitory action of this arsenical by treating sensitized guinea pigs before shock He gave intravenously 1 cc of a 1 50 dilution of the drug to different animals 5, 15, 30 and 60 minutes respectively before the second injection of antigen The minimum lethal dose of antigen, determined upon 4 animals, was found to be 0 3 cc intravenously administered All of the 4 animals treated 5 minutes before shock died as did 2 of the 4 treated 15 minutes before shock Three of the 4 animals treated 30 minutes before shock and all the of 4 animals treated 1 hour before also died Parallel experiments with passive anaphylaxis, in which the above mentioned dosage of drug was given, showed that 3 of the 4 animals treated 15 minutes before shock lived as well as 2 of the 4 animals treated 30 minutes before shock These experiments in passive anaphylaxis are of doubtful value on account of the small number of control animals The protective action obtained by Brodin and Huchet by adding sodium formaldehyde sulphoxylate to the second injection of antigen may be cited here

Nephrectomy

Pistocci, in 1920, could not find that nephrectomy had any influence on anaphylactic shock Details of his experiments are lacking

"Novoprotin" and "Novoprotein"

Rysznyák and Korányi, in 1927, obtained evidence of inhibition of shock with "Novoprotin" For the technique of the experiments, please see "Cascosan"

Schneider, in 1927, obtained no inhibition of shock by giving animals both radiation and subcutaneous injections of "Novoprotein" His experiments are not comparable with those of Rysznyák and Korányi, because of the differences in method

Olive oil

Achard and Flandin, in 1911, gave injections of from 5 to 20 cc of olive oil before the injection of antigen without any protection

Opium

Besredka, in 1907 c, found that 1 cc of 1 per cent opium, although causing narcosis, had no inhibitory action upon shock

Orange juice

See Vitamin C

Oxygen

Anderson and Schultz, in 1909, gave artificial respiration with oxygen before the shocking dose of antigen and found that of their 16 treated guinea pigs, 7 animals, or 43 per cent lived, as compared with 3 animals, or 18 per cent of the 16 controls Combining artificial respiration with treatment with adrenalin and a chloral hydrate urethane solution, some protection was also afforded, but the exact rôle of the oxygen in these tests cannot be determined

Pancreatin

Anderson and Rosenau, in 1908 gave 1 gram of pancreatin subcutaneously the day before shock One guinea pig was so treated and died when given 0 5 cc of the serum antigen in the brain Some of the controls were killed with 0 25 cc of antigen

Lesné and Dreyfus, in 1911, found that, in rabbits sensitized with egg white, shock could be repressed by adding pancreatin to the second injection of antigen When the antigen was actinocongestin, similar treatment caused inhibition of shock, but less than in the egg white series No protocols were given and the number of controls was not stated

Paraldehyde

Rosenau and Anderson, in 1909, gave 3 sensitized guinea pigs 0 9 or 1 0 cc of paraldehyde by mouth 1 hour before shocking them intraperitoneally with 6 cc of the serum antigen One animal died, 1 recovered after marked shock and 1 had mild shock No controls were given, but the authors concluded that the drug had but slight influence

Pepsin

Rosenau and Anderson, in 1908 (Hyg Lab Bull, No 45), obtained no inhibition of shock by giving 0 5 gram of pepsin subcutaneously 1 day before the second injection of antigen, which was 0 5 cc injected into the brain Only 1 animal was treated This was apparently the minimum lethal dose of antigen

Lesné and Dreyfus, in 1911, observed the same effects with pepsin as with pancreatin Rabbits sensitized to egg white could be protected from shock by adding pepsin to the second dose of antigen When actinocongestion was used for sensitization, similar treatment with pepsin also inhibited shock, but less strikingly than in the egg white series No protocols were given

Peptone

Anderson and Rosenau, in 1908, found that 0 2 gram of peptone given subcutaneously the day before shock caused no inhibition The antigen was injected into the brain in an amount of 0 5 cc

Biedl and Kraus, in 1909, in an article without protocols, stated their belief that peptone and the shocking dose of antigen acted in the same way, animals treated with peptone having no reaction to the antigen and vice versa

Pfeiffer and Mita, in 1910, were primarily interested in temperature variations They found in sensitized animals that if treatment consisted of the intraperitoneal injection of 0 3 gram of peptone, in a 10 per cent solution, 1 or 2 days before shock, the temperature variations after shock were from 3 2° to 4°C But if this treatment was given 3 or 12 days before shock, no temperature variation was observed upon the injection of the antigen, the 3 controls showing variations from 5° to 9°C and all dying Animals treated with 0 05 gram of peptone 3 or 4 days before shock also had much milder shock than the controls, which died The authors, therefore, seemed justified in their conclusion that anaphylactic shock could be influenced by peptone

Pfeiffer, in 1911, found that of 8 animals given 0 25 cc of 10 per cent peptone and 2 given 0 3 cc (Table 28, page 633), 7 animals had definitely less shock than the 4 controls

Kumagai and Odaira, in 1912, found that after intraperitoneal treatment with 0 03 gram of peptone per 100 grams of weight 2 pigs survived 1 or 2 lethal doses of antigen This treatment did not protect 3 animals against 3 or 4 minimum lethal doses These authors also did experiments with passive anaphylaxis Normal guinea pigs were given 0 5 cc of anti-sheep rabbit serum and 24 hours later 0 1 gram of peptone Twenty-four hours after the peptone, sheep serum was given intravenously Of the 4 treated animals, 1 survived 2 minimum lethal doses and another 4, while 1 animal each died from 5 and 10 lethal doses Unfortunately, there were only 2 controls for this interesting work on passive anaphylaxis

Heyde, in 1912, obtained less reaction in animals given peptone 3 days before the second injection of antigen than was observed in the controls No protocols of this work were given

Besredka, Ströbel and Jupille, in 1913, reported 1 experiment in which 1 5 cc of 10 per cent peptone was given two hours before shock Although the peptone itself caused a severe reaction, it failed to protect the animal from the subsequent intravenous administration of the serum antigen No emphasis can be placed on this work

Larsen, Haigh, Alexander and Paddock in 1923, obtained no inhibition of shock by giving peptone 30 minutes before the second injection of antigen, or from 5 doses of peptone during the sensitization period There was no inhibition of response in excised muscle treated with 4 cc of 4 per cent peptone Some inhibition of response, however, was obtained with 6 or 8 cc of this peptone solution and complete inhibition with 10 or more cc Of the 16 controls for the in vivo experiments, 6 died, 1 had moderate shock, 7 slight shock and 2 no shock All injections were made intracardially

Karsner and Ecker, in 1924, treated sensitized guinea pigs with 0 005 or 0 01 mgm per gram of peptone in 0 1 or 0 2 per cent solutions When the treated animals were given a shocking dose of antigen lethal for 4 controls, it was found that of 3 animals given the smaller dose of peptone 30 minutes before the antigen, 1 died and 2 had severe shock with recovery Of three animals given the larger dose of peptone 30 minutes before shock, 1 died and 2 had mild shock When treatment was given 24 hours before the second injection of antigen, 2 died and 1 recovered from severe shock in both series, i e , 3 given the smaller and 3 the larger dosage of peptone The authors interpreted these results as indicating that peptone protected for at least half an hour, but that this action had almost entirely disappeared in 24 hours In view of the fact that the variation was only 1 pig in each set, that is, treating 30 minutes before 1 of 3 died, and treating 24 hours before 2 of 3 died in each set, such general conclusions do not seem statistically justified without a much larger series

Summary Of the favorable reports on the inhibitory action of peptone, those of Pfeiffer and Mita, and of Pfeiffer offer the most convincing evidence The studies of Karsner and Ecker, of Kumagai and Odaira and of Brodin and Huchet are less conclusive because of the smaller series used, while the articles by Heyde and by Biedl and Kraus are entirely lacking in protocols Of the unfavorable reports, those of Rosenau and Anderson and of Besredka, Strobel and Jupille are extremely limited in the number of animals used The work of Larsen, Haigh, Alexander and Paddock is carefully controlled and shows no inhibition of shock by treating sensitized animals with peptone They did, however, obtain inhibition of response by adding large enough amounts of peptone to the solution used for the suspension of excised muscle In short, there is some, but not striking evidence that peptone may inhibit shock within certain defined limits

Pilocarpine hydrochloride

Levy Solal and Tzanck, in 1923 gave intracardially 1 mgm of pilocarpine hydrochloride per 500 grams of body weight simultaneously with the shocking dose

Pepsin

Rosenau and Anderson, in 1908 (Hyg Lab Bull, No 45), obtained no inhibition of shock by giving 0 5 gram of pepsin subcutaneously 1 day before the second injection of antigen, which was 0 5 cc injected into the brain Only 1 animal was treated This was apparently the minimum lethal dose of antigen

Lesné and Dreyfus, in 1911, observed the same effects with pepsin as with pancreatin Rabbits sensitized to egg white could be protected from shock by adding pepsin to the second dose of antigen When actinocongestion was used for sensitization, similar treatment with pepsin also inhibited shock, but less strikingly than in the egg white series No protocols were given

Peptone

Anderson and Rosenau, in 1908, found that 0 2 gram of peptone given subcutaneously the day before shock caused no inhibition The antigen was injected into the brain in an amount of 0 5 cc

Biedl and Kraus, in 1909, in an article without protocols, stated their belief that peptone and the shocking dose of antigen acted in the same way, animals treated with peptone having no reaction to the antigen and vice versa

Pfeiffer and Mita, in 1910, were primarily interested in temperature variations They found in sensitized animals that if treatment consisted of the intraperitoneal injection of 0 3 gram of peptone, in a 10 per cent solution, 1 or 2 days before shock, the temperature variations after shock were from 3 2° to 4°C But if this treatment was given 3 or 12 days before shock, no temperature variation was observed upon the injection of the antigen, the 3 controls showing variations from 5° to 9°C and all dying Animals treated with 0 05 gram of peptone 3 or 4 days before shock also had much milder shock than the controls, which died The authors, therefore, seemed justified in their conclusion that anaphylactic shock could be influenced by peptone

Pfeiffer, in 1911, found that of 8 animals given 0 25 cc of 10 per cent peptone and 2 given 0 3 cc (Table 28, page 633), 7 animals had definitely less shock than the 4 controls

Kumagai and Odaira, in 1912, found that after intraperitoneal treatment with 0 03 gram of peptone per 100 grams of weight 2 pigs survived 1 or 2 lethal doses of antigen This treatment did not protect 3 animals against 3 or 4 minimum lethal doses These authors also did experiments with passive anaphylaxis Normal guinea pigs were given 0 5 cc of anti-sheep rabbit serum and 24 hours later 0 1 gram of peptone Twenty-four hours after the peptone, sheep serum was given intravenously Of the 4 treated animals, 1 survived 2 minimum lethal doses and another 4, while 1 animal each died from 5 and 10 lethal doses Unfortunately, there were only 2 controls for this interesting work on passive anaphylaxis

Heyde, in 1912, obtained less reaction in animals given peptone 3 days before the second injection of antigen than was observed in the controls No protocols of this work were given

Besredka, Strobel and Jupille, in 1913, reported 1 experiment in which 1 5 cc of 10 per cent peptone was given two hours before shock Although the peptone itself caused a severe reaction, it failed to protect the animal from the subsequent intravenous administration of the serum antigen No emphasis can be placed on this work

Larsen, Haigh, Alexander and Paddock in 1923, obtained no inhibition of shock by giving peptone 30 minutes before the second injection of antigen, or from 5 doses of peptone during the sensitization period There was no inhibition of response in excised muscle treated with 4 cc of 4 per cent peptone Some inhibition of response, however, was obtained with 6 or 8 cc of this peptone solution and complete inhibition with 10 or more cc Of the 16 controls for the in vivo experiments, 6 died, 1 had moderate shock, 7 slight shock and 2 no shock All injections were made intracardially

Karsner and Ecker, in 1924, treated sensitized guinea pigs with 0 005 or 0 01 mgm per gram of peptone in 0 1 or 0 2 per cent solutions When the treated animals were given a shocking dose of antigen lethal for 4 controls, it was found that of 3 animals given the smaller dose of peptone 30 minutes before the antigen, 1 died and 2 had severe shock with recovery Of three animals given the larger dose of peptone 30 minutes before shock, 1 died and 2 had mild shock When treatment was given 24 hours before the second injection of antigen, 2 died and 1 recovered from severe shock in both series, i e , 3 given the smaller and 3 the larger dosage of peptone The authors interpreted these results as indicating that peptone protected for at least half an hour, but that this action had almost entirely disappeared in 24 hours In view of the fact that the variation was only 1 pig in each set, *that is, treating 30 minutes before 1 of 3 died, and treating 24 hours* before 2 of 3 died in each set, such general conclusions do not seem statistically justified without a much larger series

Summary Of the favorable reports on the inhibitory action of peptone, those of Pfeiffer and Mita, and of Pfeiffer offer the most convincing evidence The studies of Karsner and Ecker, of Kumagai and Odaira and of Brodin and Huchet are less conclusive because of the smaller series used, while the articles by Heyde and by Biedl and Kraus are entirely lacking in protocols Of the unfavorable reports, those of Rosenau and Anderson and of Besredka, Ströbel and Jupille are extremely limited in the number of animals used The work of Larsen, Haigh, Alexander and Paddock is carefully controlled and shows no inhibition of shock by treating sensitized animals with peptone They did, however, obtain inhibition of response by adding large enough amounts of peptone to the solution used for the suspension of excised muscle In short, there is some, but not striking evidence that peptone may inhibit shock within certain defined limits

Pilocarpine hydrochloride

Levy Solal and Tzanck, in 1923 gave intracardially 1 mgm of pilocarpine hydrochloride per 500 grams of body weight simultaneously with the shocking dose

of antigen by the same route All of the 3 guinea pigs so treated lived and the 6 controls died Three other pigs were given the same dose of pilocarpine a few minutes before the intracardial injection of the shocking dose of antigen Two lived and 1 died The author made a general statement that other pilocarpine salts, especially pilocarpine nitrate were without effect

Stoland and Sherwood, in 1923, in their experiments with excised uterine muscle found that pilocarpine exerted the same stimulation of the sensitized muscle as the antigen

Pituitrin

Moldovan and Zolog, in 1923, found that pituitrin, given after China ink and 30 minutes before shock, did away with the protective action of the ink

Potassium chlorate

Belin, in 1911, in a very small series, in which there was usually only 1 control and 1 treated animal for each variation, studied the action of potassium chlorate in guinea pigs sensitized with ass serum Both controls died, but animals survived that had been treated with from 1 to 4 injections of 2 to 5 centigrams of calcium chlorate subcutaneously The shocking dose of antigen was given intracerebrally In other experiments, 0 25 cc of antigen was given intravenously Two controls so injected died One treated animal received subcutaneously 2 doses of 5 centigrams of drug 2 and 4 hours before shock Another received 10 centigrams of drug by mouth two hours before shock Both treated animals lived One animal each treated with 1 or 1 5 cc of a 1 per cent solution of potassium chlorate, method of administration not stated, given 2 minutes after the shocking dose of antigen lived Other similar tests were done, but it is impossible to evaluate the results on account of the small number of animals used and the incompleteness of the protocols There was, however, some evidence that potassium chlorate might inhibit shock It is possible that a study of larger series would entirely change the findings

Potassium ovalate

Anderson and Rosenau, in 1908, found that 1 gram of this drug, injected subcutaneously, had no effect when given the day before the shocking dose of antigen, which was 0 5 cc of horse serum, administered intracranially Only 1 animal was treated The amount of antigen used was apparently the minimum lethal dose

Potassium permanganate

Rosenau and Anderson, in 1906, added 3 cc of a 1 per cent solution of potassium permanganate to 25 cc of serum The mixture was kept for 40 hours at 15°C and filtered Three cubic centimeters of the filtrate killed the 1 animal tested

Belin, in 1911, gave 1 sensitized guinea pig 2 centigrams of potassium per-

manganate subcutaneously, 1½ hours before the injection of 2 lethal doses of antigen The animal had acute shock, but recovered The 1 control died Another animal, given 0 5 cc of a 1 per cent solution of drug 2 minutes *after* the shocking dose of antigen also lived, while two controls died

Pregnancy

J Duran Reynalls, in 1920, is cited by Lumiere and Couturier, 1922, for his statement that sensitized females seemed to lose their sensitivity during gestation

Lumière and Couturier, in 1921, found that while males die in shock after the second injection of antigen, 0 6 cc , given intracardially, pregnant females had no marked shock After delivery, sensitivity reappeared No protocols were given and the number of animals used was not stated

Lumière and Couturier, in 1922, found that pregnant guinea pigs were resistant to anaphylactic shock and to shock from other causes The authors introduced ovules of sterile rubber of the volume of the uterine sac into the peritoneal cavity and failed to inhibit shock From this they concluded that pressure was not the cause of the inhibition in pregnancy No inhibition was obtained by castration or administration of sexual gland extracts This protection the authors finally attributed to the increase in blood volume which occurs in pregnancy No protocols were given

Pierret and Crampon, in 1923, noted the absence of shock in gravid guinea pigs, but gave no details

Summary No definite proof has been offered that animals are desensitized during gestation, although the findings of all of those who have studied this aspect of the problem are in agreement It is unfortunate that details are lacking

Pressure

See "Pregnancy" *Lumière* and *Couturier*, 1922

Quinine

M I Smith, in 1920, found that the subcutaneous administration of quinine to sensitized guinea pigs before the administration of the shocking dose of antigen increased their susceptibility to shock

Rice, polished

See "Vitamin B"

Roentgen ray

Rosenau and Anderson, in 1906, treated the serum used for the shocking dose of antigen with 40 amperes at 4 inches for 40 minutes without modifying its toxicity

Von Heinrich, in 1913, found that 6 guinea pigs, given an erythema dose of radiation, 3 Kalom, on the day of sensitization, lived when shocked 21 days later,

while the 2 controls died Similarly 1 of 2 animals was protected against 2 minimum lethal doses of antigen, and 1 of 2 against 3 lethal doses, but no protection was obtained against larger amounts of antigen Treatment with 3 Kalom given 8 days after sensitization seemed to have protected 2 animals One of 2 animals was protected when this treatment was given 14 days after sensitization No protection was obtained treating 3 hours before shock Two guinea pigs, irradiated 14 days before sensitization, survived amounts of antigen lethal for 2 controls These experiments throughout, however, were insufficiently controlled, no allowance being made for individual variation in the animals An interesting experiment was done in passive anaphylaxis by irradiating 2 guinea pigs 3 weeks after their sensitization, transferring their sera to normal animals which then had no shock when given antigen, while both of the controls were shocked

Corper, Black and Moore, in 1922, found roentgen ray treatment without effect A maximum non-lethal irradiation had no inhibitory action when given 7 days before sensitization, at the time of sensitization, or 7 days before or on the day of the second injection of antigen Nor was any inhibition obtained by giving repeated small or medium exposures before and during sensitization

Schneider, in 1927, obtained protection by radiation with a lethal exposure on the day of sensitization or on the 1st and 2nd days thereafter No protection was obtained with the same treatment during the rest of the sensitization period, or with smaller amounts of radiation Combining radiation with subcutaneous injections of lecithin or of novoprotein gave no protection in the 3 animals so treated

Summary Radiation of the antigen used for shock was found valueless by Rosenau and Anderson Evidence that exposure of the experimental animals before or at the time of sensitization protects them from subsequent shock has been offered by von Heinrich and by Schneider, although Corper and his associates were unable to demonstrate such an inhibition Neither von Heinrich nor Corpor, Black and Moore obtained any evidence of inhibition of shock by exposure to Roentgen ray during the incubation period

Saponin

Kopaczewski and Vahram, in 1919, made a general statement that anaphylactic shock could be inhibited by lowering the surface tension of the blood by an injection of an 0 5 per cent solution of saponin

Seed extracts

Isaacs, in 1924, worked with seed extracts, or "Proteogens" Of 5 lots of control animals, 20 died and 7 recovered when the shocking dose of antigen was 1 cc of 10 per cent egg white given intraperitoneally Of the guinea pigs treated with extract no 1, 0 015 to 0 25 cc from 4 to 24 hours before shock, 40 animals died, 2 of these having been starved for 24 hours, and 33 recovered Treating with extract no 2, 0 1 to 1 cc 4 injections, 2 days apart, the last 48 hours before

shock, 2 animals died and 1 lived When 5 injections were given 24 hours apart, the results were the same Giving single treatments from 30 minutes to 6 hours before shock, 22 animals died and 13 lived The author concluded that seed extracts produced partial desensitization in over 50 per cent of the animals The treated animals that died behaved like the controls The treated animals that survived also showed some shock symptoms, but less than the controls Isaacs also believed that there was an optimum for each extract and that desensitization, developing during the first hour after treatment, lasted for 24 hours or longer

Serum fractions

Besredka, in 1908, found that 0 25 cc of "petit serum," given intraperitoneally a few hours before the second injection of the whole serum antigen, protected guinea pigs Such protection was obtained with serum treated with 2 parts of alcohol to 1 of serum at 90°C , precipitated with physiological water and filtered or dialyzed Treatment by rectum and large doses by mouth were also effective

Dale and Hartley, in 1916, found that "An effective dose of any of the proteins to which the guinea pig plain muscle has been sensitized partially or completely desensitized it to the other proteins of the same serum "

Suarez, in his first paper, in 1928, demonstrated the separate antigenic action of pseudoglobulin, of euglobulin and of serum albumin

Suarez and Schaefer, in 1928, sensitizing guinea pigs with whole serum and treating them with serum fractions, found that in the series given from 1 to 3 injections of euglobulin from 1 to 4 days before shock, none of the 3 treated animals lived One animal given 0 25 cc of pseudoglobulin intra arterially 2 days before shock survived 2 lethal doses, while another animal, given 2 injections of serum deprived of euglobulin, 5 minutes later survived 4 lethal doses of whole serum Animals given 1 injection of serum albumin, 1 with toxic and 4 with atoxic preparations, all survived from 2 to 8 lethal doses, treatment being given in amounts of from 0 5 to 3 cc , by various routes No protocols for the controls were given, but evidently the lethal dose had been determined

Three animals, sensitized with euglobulin and desensitized with pseudoglobulin or serum albumin, lived after receiving 2 or 5 lethal doses of euglobulin Two animals specifically desensitized with euglobulin died after receiving 1 to 2 lethal doses Three animals, sensitized with pseudoglobulin, and treated with from 1 to 2 cc of serum albumin or euglobulin survived 1 or 2 lethal doses Of the 2 animals specifically desensitized with 0 25 cc of pseudoglobulin, 1 survived 2 lethal doses and 1 died after 4 Animals sensitized with serum albumin and treated with pseudoglobulin or euglobulin, survived 4 and 2 lethal doses respectively, while the one given serum albumin as a control survived 3 lethal doses

Summary There is some evidence that the administration of serum fractions will inhibit shock The evidence is not entirely conclusive on account of the small number of animals used and of the lack of protocols

Serum globulin

Bauer, in 1912, sensitized guinea pigs with 1 cc of whole milk intraperitoneally and 36 days later treated 5 of them with from 0 01 to 5 cc of beef serum globulin intraperitoneally The next day they received 4 cc of casein intravenously Two controls, given the same amount of antigen died The 5 treated animals lived, but were shocked

Serum, heterologous

Rosenau and Anderson, in 1906, obtained little or no protection by giving horse serum to guinea pigs previously sensitized with dog, hog, beef, sheep, cat or rat serum With 1 exception these animals all had shock upon the subsequent injection of the specific antigen

Pfeiffer and Mita, in 1910, studied the effect of the injection of an heterologous serum upon the temperature drop observed in sensitized guinea pigs after the administration of small shocking doses of antigen In 1 set of 5 animals, with 1 control, 2 cc of heterologous serum, given intraperitoneally just prior to the specific antigen, might have accounted for the stability of the temperature curve The temperature of the 1 control dropped 3 6°C

Ascoli, in 1910, sensitized guinea pigs to anti-diphtheria horse serum From 14 to 75 days later, he injected retro-ocularly or intracerebrally 0 2 cc of anti-diphtheria sheep serum and about 50 per cent of the animals lived With these as controls, he then essayed the same type of experiment with another set and obtained better results, as all of his animals lived From 15 minutes to 6 hours after this second injection, he gave intracerebral injections of normal horse serum, to determine whether or not his animals had been desensitized by the sheep serum and found that 3 of the 5 animals lived This was hardly a conclusive experiment In another series, he sensitized animals with normal sheep serum, desensitized them with 0 2 to 0 5 cc of horse serum, given either intra-ocularly or intracerebrally and then found that a second injection of sheep serum killed only 29 per cent Unfortunately Ascoli had no controls for this experiment, which otherwise would have been of value

Calvary, in 1911, sensitized dogs to horse serum and gave them beef serum before the second injection of antigen, so protecting the animals from shock The controls were not given

Benjamin and Witzinger, in 1911, carried out a series of experiments in which horse serum was given 24 hours before shock to animals sensitized with beef serum It was found that while 5 or 62 5 per cent of the 8 controls died and 2 had severe shock with recovery, of the 17 treated animals, 7 or 41 1 per cent died and 4 had severe shock with recovery The series in which treatment was given 3 or 4 days before shock had only 1 control

Weil, in 1913, brought out an excellent piece of work His number of control animals was small, but they died, having received substantially smaller doses of antigen than the treated animals that lived His work may be divided into two parts, dealing with, first, passive sensitization and, second, active sensitization

The daily injection of several large doses of normal sheep serum and normal rabbit serum into guinea pigs prior to the administration of immune rabbit serum (horse) protected the animals against passive sensitization The author did not show how much protection was gained This protection was manifest within 1 to 2 days after preliminary treatment had ended and continued for at least two weeks

"When pigs are actively sensitized with normal horse serum they are not desensitized by 3 successive injections of 3 cc of sheep serum given subcutaneously at the end of the period of incubation" In this experiment he used 6 animals They were shocked with 0 2 to 0 3 cc of antigen and all died, the controls dying after 0 1 to 0 2 cc of antigen, always given intravenously

Brack, in 1921 stated that the injections of an heterologous serum in highly sensitized animals could produce anaphylactic shock This non specific shock was less than the specific, but could cause a lowering of sensitivity to the homologous serum He used Massini's technique of studying excised muscle

Karsner and Ecker, in 1922, tried the effect of giving various dosages of heterologous sera at different times before the shocking dose of antigen Sensitization was with either human or horse serum Horse, beef, human and hog sera were given intraperitoneally and subcutaneously for treatment The animals were divided into 5 sets of 10, 16, 9, 8 and 9 pigs Four of these sets had two controls and the other set had one The controls cannot be grouped as the experiments were done on different days and at various intervals after sensitization It seems superfluous to insist upon more than this number of controls per set Out of 43 treated animals, 29 lived and 14 died, but as in each set 3 or 4 various methods of desensitization were attempted and as time intervals varied not only between the sets but among the animals in the same set, there are too few animals to permit conclusions to be drawn, although this work is certainly interesting and suggestive

Summary No critical piece of work has been done which conclusively demonstrates that heterologous sera, injected before the shocking dose of antigen, will completely or partially protect against specific shock animals which have been actively sensitized with one protein The work of Karsner and Ecker cannot be accepted as they have no adequate controls In passive desensitization the work of Weil is of importance and should be repeated He has shown that passively sensitized animals may be desensitized by the injection of heterologous sera

There is also no definite work except that of Rosenau and Anderson, showing that protection is not to be gained by the injection of non specific sera before the second dose of antigen The work of Ascoli and Calvary does not offer conclusive evidence on either side, nor does that of Brack indicate that heterologous serum may actually cause shock

Normal serum

See also Heterophile Antigen

Friedberger and Hartoch, in 1909, obtained no protection by giving sensitized guinea pigs 2 cc of normal guinea pig serum just before shock with what was probably several lethal doses of antigen

Dale and Kellaway, in 1923, partially protected 1 guinea pig from shock by giving normal serum 70 minutes before the second injection of antigen

Weil, in 1914, made further studies of his interesting observations that from 1 to 6 cc of normal rabbit serum would protect an animal against passive sensitization with anti-rabbit immune serum This reaction was not specific and human serum, given in this way, protected against anti-rabbit and other sera This phenomenon Weil called "anti-sensitization" in distinction from desensitization or anti-anaphylaxis He also found that guinea pigs, sensitized with sheep serum, had no reaction to or desensitization by normal rabbit serum Animals sensitized with human ascitic fluid had no marked reaction to normal rabbit serum, but could be desensitized by it for 3 days

Kellaway and Cowell, in 1922, sensitized guinea pigs with horse serum albumin and endeavored to desensitize them with pooled normal guinea pig serum Three controls given the minimum lethal dose died Of the 6 treated animals, 2 received 3 cc of normal serum before the shocking dose of antigen Of these 1 survived 2 minimum lethal doses and 1 died after 4 minimum lethal doses Animals were then given 3 cc of serum 2, 3½ and 22 hours before the minimum lethal dose, or multiples thereof The animals given 4 lethal doses 2 hours after treatment died, whereas the pig given 2 lethal doses 3½ hours after treatment had no shock Twenty-two hours after treatment, 1 pig had slight shock from 1 lethal dose and 1 pig died from 2 lethal doses The series was too small for very definite conclusions but the paper is of interest and should be confirmed The authors concluded that the maximum protection was obtained by treatment 1 hour before the shocking dose of antigen

Summary The work of Weil, less conclusively corroborated by that of Kellaway and Cowell, offers strong evidence that normal serum may inhibit shock under certain conditions Normal serum controls should be made in all studies where any type of serum is used for treatment

Sodium bicarbonate

Kopaczewski and Roffo, in 1920, had no shock in sensitized guinea pigs treated with 5 cc of 10 per cent sodium bicarbonate intravenously or with 10 cc of a 10 per cent solution given subcutaneously, either 30 or 60 minutes before the shocking dose of antigen Only 1 control was made so that the findings were not conclusive

Eggstein, in 1921, contributed an excellent paper, quite the best of them all in our opinion, as the experiments were sufficiently controlled and the series sufficiently large to allow conclusions to be drawn Treatment consisted of 0 1, 0 3 or 0 4 gram of drug given intravenously to sensitized guinea pigs from 10 to 20 minutes before the shocking dose of antigen While all of the controls given comparable amounts of antigen died, the mortality among the treated animals was from 78 5 to 92 8 per cent, that is, there was a definite balance in favor of the treated animals It is possible that the amount of the shocking dose of antigen was unnecessarily large

Arloing and Vaulhey, in 1921, found that 0 5 per cent sodium bicarbonate injected for 10 or 20 days during sensitization, could inhibit shock The series, however, was small and there were not enough controls The shocking dose of antigen, 0 25 cc of serum, was injected into the sub arachnoid space

Combiesco and Brauner, in 1928, studied the desensitizing action of saturated solutions of bicarbonate of soda in passive local anaphylaxis of the rabbit They obtained weaker skin reactions in sensitized animals after 10 cc of saturated solutions of sodium bicarbonate had been given intravenously, or when the drug was given by mouth, than in the controls The antigen was administered intradermally

Summary All four articles, 3 dealing with general shock and 1 with skin sensitization have given evidence of the inhibitory effect of sodium bicarbonate on shock Two of the studies, the paper of Combiesco and Brauner on skin reactions and the general paper of Eggstein were sufficiently controlled to warrant the conclusions

Sodium carbonate

Kopaczewski and A H Roffo, in 1920, found that 3 cc of a 50 per cent solution of sodium carbonate given intravenously, or 5 cc of this concentration injected subcutaneously 30 minutes before shock, inhibited anaphylaxis No protection was obtained by the intravenous injection of 5 cc of a 10 per cent solution or when 5 cc of the 50 per cent solution was given subcutaneously 2 hours before shock Only 1 control was given for entire experiment

Sicard and Paroff, in 1921, found that 12 guinea pigs, given 1 cc of a 10 per cent solution of sodium carbonate intracardially just before the intracardial injection of the second dose of antigen, had no shock Of the 12 untreated controls given the shocking dose of antigen in the same way, 9 died at once and 3 had shock, but recovered Results were less conclusive in the series of 3 animals given sodium carbonate after the second injection of antigen, at the onset of shock, as two of these animals recovered and 1 died

Sicard and Paroff, in 1921, in experiments without protocols or controls concluded that the intravenous injection of 2 5 per cent sodium carbonate or the addition of 0 3 to 0 4 gram of the drug to serum given intravenously would prevent serum sickness

Sodium chloride

Heilner, in 1908, conducted a few experiments in rabbits which had a sensitization of period of from 1 to 3 months Treatment was with 4 per cent salt solution, given to 4 rabbits, 3 of which apparently died from the toxic effects of the salt The technique employed made the experiments not comparable with those of others

Friedberger and Hartoch, in 1909, studied the effect of small and large doses of sodium chloride upon shock Of the two series of experiments with small

Arloing and Vauthy, in 1922, in their third paper, found that diluting 0 25 cc of the serum antigen with 0 75 cc or with 4 75 cc of 0 7 per cent salt solution had no inhibitory effect in the 2 guinea pigs so treated These were primarily controls for similar experiments with mineral water

Karsner and Ecker, in 1924, in their study of the colloidal inhibition of shock made the general statement that "large doses of salt solution were effective, but in the small number tried, not so much so as is kephalin "

Wedgewood and Grant, in 1924, showed that 4 young rats, kept on salt-free diet during sensitization, did not respond more to the second injection of antigen than did the 8 controls

Summary Of the reports which indicate some inhibitory action of sodium chloride, the most conclusive are the series of animals given large doses of salt reported by Friedberger and Hartoch, confirmed by Loewit, the report of Friedberger and Langer on giving salt by mouth, Ritz' paper and the study of Richet, Brodin and Saint Girons on the dilution of the shocking dose of antigen with salt The unfavorable reports are those of Armand-Delille and Launcy, who used a very small series of animals, as did Arloing and Vauthy The papers by Heilner, by Galambos and the series of animals given small doses of salt reported by Friedberger and Hartoch cannot be evaluated It seems evident, therefore, that under certain conditions, anaphylactic shock may be inhibited by sodium chloride

Sodium citrate

Rosenau and Anderson, in 1906, obtained no inhibition of shock by adding this drug to the second dose of serum One per cent of the drug was added to the whole blood at the time of bleeding Six cubic centimeters of such citrated serum killed both animals tested, but this may have been many lethal doses

Van de Carr, Lyons and Williams, in 1928, found that 2 per cent sodium citrate, given intravenously to sensitized guinea pigs, altered the colloidal state of the blood sufficiently to greatly increase the degree of anaphylactic shock

Sodium cyanide

Amberg and Knox, in 1912, sensitized rabbits by combined intravenous and intracutaneous injections of horse serum and studied sodium cyanide for its oxidative effect They found that it caused an initial increase in the reaction which later became less distinct

Sodium formaldehyde-sulphoxylate

Brodin and Huchet, in 1921, sensitized guinea pigs with horse serum and found that 1 month later a second injection of 1 cc of undiluted serum given intracardially, killed 4 of the animals This seems a very high dose of antigen to employ by this route The remaining 18 animals received increasing amounts of drug added to the shocking dose of antigen At a concentration of 25 per cent of drug in 1 cc of serum, only 1 animal in 11 died At lower concentrations, more

animals died Similar results were obtained in dogs This work is worthy of consideration The authors were able to give as high as 1 gram per kilo to rabbits without ill effects The relation of this drug, CH OH—SO_2Na to novarsenobenzol should be considered in view of the inhibitory effect of the latter

Sodium glycocholate

Kopaczewski and Vahram, in 1919, found that shock could be suppressed by the injection of 1 cc of a 1 per cent solution of sodium glycocholate The number of controls was not stated

Sodium hydroxide

Ambert and Knox, in 1912, used this to control experiments with sodium cyanide and found more reaction with the cyanide than with the hydroxide

Doerr, in 1912, cited without reference other work with sodium hydroxide which we have been unable to trace

Sodium hyposulphite

Lumière and Chevrotier, in 1920, found that their control group of sensitized animals, the number of which was not stated, all died after the second injection of the serum antigen, 0 5 cc which, with 0 5 cc of physiological salt solution, was injected intracardially When 0 5 cc of 5 per cent sodium hyposulphite was used to dilute the antigen instead of salt solution, none of the animals had shock symptoms The number treated was not given The same results were obtained in a confirmatory series

Sodium iodoxybenzoate

Amberg and Knox, in 1912, working with skin tests in sensitized rabbits found that 10 cc of N/20 iodoxybenzoic acid, given intravenously, caused a diminution of the skin reaction Controls with iodbenzoic acid and benzoic acid, showed no reduction

Sodium nitrite

Anderson and Rosenau, in 1908, found that the subcutaneous administration of this drug had no inhibitory effect One guinea pig had 0 3 gram of the drug and 1 had 0 025 gram 3 minutes before 1 cc of the serum antigen was given intraperitoneally Both animals died The drug was used on account of its methaemaglobin production

Sodium oleate

Jobbling and Petersen, in 1914, found that sub lethal doses of soap solutions, injected simultaneously with the second injection of antigen prevented shock This inhibition was obtained with serum albumin, but not when the antigen was whole serum

Kopaczewski and Vahram, in 1919, treated 8 sensitized guinea pigs with intravenous injections of sodium oleate, given 5 minutes before shock Two of the animals died, and the rest had mild or no shock An unstated number of controls died after 0 3 cc of antigen The treated animals received 0 5 cc

Sodium persulphate

Belin, in 1911, found that 1 injection of 5 centigrams of this drug subcutaneously caused sensitized guinea pigs to die faster than the controls when shocked The number of animals treated was not stated and the number of controls was inadequate

Sodium sulphate

Anderson and Rosenau, in 1908, obtained no inhibition of shock by giving 0 1 gram of this drug subcutaneously the day before the shocking dose of antigen, which was 0 5 cc of serum, injected into the brain Only 1 animal was treated

Sodium taurocholate

Kopaczewski and Vahram, in 1919, believed that they could suppress shock by injecting 1 cc of a 1 per cent solution of sodium taurocholate The theory of its action was that of lowering the surface tension of the blood

Splenectomy

Pistocchi, in 1920, could not find that splenectomy had any influence on anaphylactic shock He gave no details, as to antigen, time of operation or the number of animals used

Smitch, in 1926, considering splenectomy a satisfactory method of blocking the reticulo-endothelial system, failed to obtain any protection in animals splenectomized 1 week before sensitization and treated with either China ink or iron oxide 1 day before sensitization No determination of the minimum lethal dose of antigen was made

Klinge, in 1927, studying the Arthus phenomenon, found that splenectomy did not hinder it No protocols were given in this brief summary

Starvation

Argaud and Billard, in 1911, presented the hypothesis that inanition for several days before shock should attentuate it Their reason for this view was that they had observed a disappearance of the white blood cells in starvation, while Lassablière and Richet had noted a marked leucocytosis in sensitized animals This theory was given without confirmatory experimentation

Konstantoff, in 1912, kept sensitized animals on water only for 4 days before shock The experiments were adequately controlled and showed differences in favor of the treated animals However, the number treated in any given group was small Three antigens were used and 3 doses of each antigen

Friedberger and Langer, in 1912, failed to protect 2 sensitized guinea pigs starved before shock, but did get protection if starvation and salt treatment were combined, and inanition being entirely unnecessary

Pierret and Crampon, in 1923, found that while their untreated controls died at once after the intravenous injection of 1 cc of undiluted serum antigen, the animals fasted for 36 hours before the same amount of antigen had slight shock, none dying The same results were obtained with guinea pigs given for several weeks a "regime carancé," i e , almost entirely dry hay Only a brief note was presented, without protocols or information as to the number of animals studied

Zolog, in 1924, disagreed with Pierret and Crampon, finding no difference in the degree of shock in guinea pigs on a normal diet and those kept on water only for 24 and 48 hours before shock The minimum lethal dose of antigen was calculated per 100 grams of weight of animal, a fallacious method

Summary There is no entirely conclusive work to show that starvation can modify shock The work of Konstantoff is by far the best, but is marred by the many variations, which reduce by too much the number of animals given any particular treatment

Stovain

Kopaczewski, Roffo and Roffo, in 1920, found that 0 25 cc of 2 per cent stovain given intravenously just before 0 5 cc of the shocking dose of antigen protected "all" of the treated animals, while "all" of the controls died

Strychnine

Doerr, in 1908, cited the use of strychnine without details

Succinic acid peroxide (alphozone)

Anderson and Rosenau, in 1906, found that 1 or 2 cc of a 10 per cent solution of this drug added to 25 cc of serum had no effect upon its toxicity

Sulphur

Arloing, Langeron, Milhaud and Ricard, in 1923, gave no details of their experiments with colloidal sulphur

Ruszyńák and Korányi, in 1927, observing temperature changes in sensitized guinea pigs, believed that the injection of sulphur, probably a protein compound inhibited shock The technique of these experiments is given under "Cascosan"

Surgical interference, general

See also Adrenalectomy, Brain Surgery, Nephrectomy, Splenectomy, Thymectomy, Thyroidectomy and Vagus Section

Dale, in 1912–13, found that excluding the abdominal viscera and the brain from the circulation did not inhibit anaphylactic response of the bronchioles of sensitized guinea pigs

Kopaczewski and Vahram, in 1919, treated 8 sensitized guinea pigs with intravenous injections of sodium oleate, given 5 minutes before shock Two of the animals died, and the rest had mild or no shock An unstated number of controls died after 0 3 cc of antigen The treated animals received 0 5 cc

Sodium persulphate

Behn, in 1911, found that 1 injection of 5 centigrams of this drug subcutaneously caused sensitized guinea pigs to die faster than the controls when shocked The number of animals treated was not stated and the number of controls was inadequate

Sodium sulphate

Anderson and Rosenau, in 1908, obtained no inhibition of shock by giving 0 1 gram of this drug subcutaneously the day before the shocking dose of antigen, which was 0 5 cc of serum, injected into the brain Only 1 animal was treated

Sodium taurocholate

Kopaczewski and Vahram, in 1919, believed that they could suppress shock by injecting 1 cc of a 1 per cent solution of sodium taurocholate The theory of its action was that of lowering the surface tension of the blood

Splenectomy

Pistocchi, in 1920, could not find that splenectomy had any influence on anaphylactic shock He gave no details, as to antigen, time of operation or the number of animals used

Simitch, in 1926, considering splenectomy a satisfactory method of blocking the reticulo-endothelial system, failed to obtain any protection in animals splenectomized 1 week before sensitization and treated with either China ink or iron oxide 1 day before sensitization No determination of the minimum lethal dose of antigen was made

Klinge, in 1927, studying the Arthus phenomenon, found that splenectomy did not hinder it No protocols were given in this brief summary

Starvation

Argaud and Billard, in 1911, presented the hypothesis that inanition for several days before shock should attentuate it Their reason for this view was that they had observed a disappearance of the white blood cells in starvation, while Lassablière and Richet had noted a marked leucocytosis in sensitized animals This theory was given without confirmatory experimentation

Konstantoff, in 1912, kept sensitized animals on water only for 4 days before shock The experiments were adequately controlled and showed differences in favor of the treated animals However, the number treated in any given group was small Three antigens were used and 3 doses of each antigen

Friedberger and Langer, in 1912, failed to protect 2 sensitized guinea pigs starved before shock, but did get protection if starvation and salt treatment were combined, and inanition being entirely unnecessary

Pierret and Crampon, in 1923, found that while their untreated controls died at once after the intravenous injection of 1 cc of undiluted serum antigen, the animals fasted for 36 hours before the same amount of antigen had slight shock, none dying The same results were obtained with guinea pigs given for several weeks a "regime carancé," i e , almost entirely dry hay Only a brief note was presented, without protocols or information as to the number of animals studied

Zolog, in 1924, disagreed with Pierret and Crampon, finding no difference in the degree of shock in guinea pigs on a normal diet and those kept on water only for 24 and 48 hours before shock The minimum lethal dose of antigen was calculated per 100 grams of weight of animal, a fallacious method

Summary There is no entirely conclusive work to show that starvation can modify shock The work of Konstantoff is by far the best, but is marred by the many variations, which reduce by too much the number of animals given any particular treatment

Stovain

Kopaczewski, Roffo and Roffo, in 1920, found that 0 25 cc of 2 per cent stovain given intravenously just before 0 5 cc of the shocking dose of antigen protected "all" of the treated animals, while "all" of the controls died

Strychnine

Doerr, in 1908, cited the use of strychnine without details

Succinic acid peroxide (alphozone)

Anderson and Rosenau, in 1906, found that 1 or 2 cc of a 10 per cent solution of this drug added to 25 cc of serum had no effect upon its toxicity

Sulphur

Arloing, Langeron, Milhaud and Ricard, in 1923, gave no details of their experiments with colloidal sulphur

Ruszyńdk and Korányi, in 1927, observing temperature changes in sensitized guinea pigs, believed that the injection of sulphur, probably a protein compound inhibited shock The technique of these experiments is given under "Cascosan"

Surgical interference, general

See also Adrenalectomy, Brain Surgery, Nephrectomy, Splenectomy, Thymectomy, Thyroidectomy and Vagus Section

Dale, in 1912–13, found that excluding the abdominal viscera and the brain from the circulation did not inhibit anaphylactic response of the bronchioles of sensitized guinea pigs

Manwaring, in 1910, ligated the aorta and vena cava above the diaphragm and found that the upper half of the sensitized animals generally did not react to the shocking dose of antigen He also removed the gastro-intestinal tract from the pylorus to the rectum, including the pancreas, without obtaining any protection Removal of the stomach, spleen, kidney, adrenals, ovaries and uterus also failed to protect Liver extirpation resulted, upon the second dose of antigen, in very slight shock in 7 dogs, no shock in 4 and definite but slight shock in 2 It is obvious that the primary object of these experiments was not to desensitize but to locate the site of the anaphylactic reaction

Voegtlin and Bernheim, in 1911, found that if the liver was excluded from the circulation, no shock occurred in sensitized dogs

Tallianine (terpine ozonê)

Belin, in 1911, treated a few guinea pigs with this drug and concluded that subcutaneous or intravenous injection of it inhibited shock if given before the second dose of antigen Treatment immediately after shock was thought to have prolonged life The series was too small and the controls too few to make these experiments conclusive

Temperature reduction

Friedberger and Kumagai, in 1913, immersed sensitized animals before shock for 4 minutes in water at 10°C While 0 025 cc of antigen killed 4 untreated controls, 1 of the treated animals survived this dosage, two survived twice this amount, 1 of 2 survived 0 07 cc of antigen, 1 survived 4 minimum lethal doses and one 5 The authors, therefore, concluded that there was a definite lessening of sensitivity by this treatment The series was short, but valid as far as it went In another series, the lethal dose for 4 controls was 0 0075 cc of the antigen Treatment was 3 minutes in water at 10°C before shock Of the 5 treated animals, 1 survived 2 lethal doses, and one 0 037 cc of antigen Seven and 10 lethal doses, however, killed 3 treated animals Immersion in ice water at 2°C , for 1 to 1½ minutes after shock was given to 3 animals, of these, one survived 2 lethal doses, 1 living and 1 dying after 1 lethal dose There is some evidence that the authors were justified in concluding that cooling before shock protected the treated animals, but their conclusion that cooling after treatment also protects is much less valid It should be born in mind that larger series of controls and of treated animals might have yielded entirely different results

Experiments with passive anaphylaxis showed that 4 of 7 controls died that were given 0 05 cc of sheep serum 24 hours after the intraperitoneal injection of 0 5 cc of anti-sheep serum Five of 6 other animals died that had been similarly prepared and given ice water after the sheep serum so that these results were far from striking

Thorium X

Carter, in 1919, obtained no desensitization with thorium X The drug s given after sensitization with egg white, horse serum or milk All of the ated animals in the egg white set died In the serum set, the results with thor X may have been worse than the controls In the milk series, the controls ed.

Crasseant, Gulup and Poiro' Delpech, in 1913, attributed the desensitizing action mineral water to the presence of radio active substances The authors gave evidence for this theory

Thymectomy

Parker and Ballif, in 1923, sensitized 4 thymectomized animals with 0 02 centi ams of sheep serum Twenty days after sensitization, these 4 animals and 5 trols received 0 1 cc of shocking antigen All of the animals were severely cked, all of the treated animals died and 1 of the controls lived This work as repeated with similar results In another paper, 1923, these authors cited periments in which no protection was obtained in 10 thymectomized guinea gs, which had been sensitized 20 days after operation

Thyroidectomy

Pozzeh, in 1920, found that thyroidectomy would give protection against anaphylaxis in about 50 per cent of his animals He gave no details as to dosage type of antigen, or as to the time of operation

Levenberg and Kepinow, in 1922, from clinical observations concluded that the thyroid gland had some relation to certain aspects of immunity Following thyroidectomy guinea pigs were sensitized with 1 cc of 1 per cent serum subcutaneously The controls (number not stated) were killed with 1 cc of 10 per cent serum given by way of the carotid artery Of the 8 thyroidectomized animals, 6 had very little if any shock and lived One of the 2 that died was found to have remaining fragments of thyroid tissue

Removal of one half or more of the thyroid gland had no effect upon sensitization No more did thyroidectomy after sensitization The work of these authors was well controlled and seems valid

Pfeiffer and Landsberg, later in 1922, showed that if thyroidectomized guinea pigs received an homologous or heterologous immune serum, they would go into fatal anaphylaxis upon receiving the specific antigen However, a thyroidectomized guinea pig or rabbit, after an injection of horse serum, was unable to elaborate a substance which would confer passive sensitization on other animals This work was also well controlled

Hopkins, in 1922 fed thyroidectomized guinea pigs on thyroid extract during the period of sensitization. Six of them died in shock after the second dose of antigen, consisting of 1 cc of a 1 10 dilution of serum Three thyroidectomized animals, that had received no thyroid extract had not the slightest shock

The work of *Kêpınow* (1922), ın whıch thyroıdectomızed gumea pıgs were gıven thyroıd extract has been referred to under Thyroıdectomy

Kêpınow, ın 1923, concluded that weak doses of thyroıd gland per os the day of shock were of no value, the same doses attenuatıng shock ıf gıven 2 days before Larger doses of thyroıd gland extract, however, augmented shock The experiments were controlled and seem valıd, although the number of animals used for each varıatıon of treatment was small The author believed that the actıon of the thyroıd ınfluenced the formatıon of anaphylactıc antıbodıes

Toxıns

Bıllard and Barbès, ın 1913, stated wıthout experımental evıdence that poısons selectıve for the nervous system, such as venoms, tetanus toxın, etc , could attenuate anaphylactıc shock

Transfusıon

Manwarıng, ın 1910, found that sensıtızed dogs, bled and gıven 1200 cc of normal dog blood, stıll reacted to the shockıng dose of antıgen

Trıkresol

Roscnau and Anderson, ın 1906, obtaıned no ınhıbıtıon of shock by addıng 0 4 per cent of trıkresol to the second dose of serum Thıs was used wıth ether as a preservatıve of the serum

Trypan blue

Isaacs, ın 1925, gave trypan blue to gumea pıgs 10 days before sensıtızatıon and durıng the sensıtızatıon perıod wıthout effect on shock He therefore concluded that a dıfferent mechanısm was ınvolved ın the productıon of anaphylactıc sensıtızatıon than ın the formatıon of antı-sheep hemolysıs, as experıments ın the productıon of haemolysın had shown that ıt was reduced ın dye treated anımals No protocols were gıven

Lewıs and Loomıs, ın 1926, concluded that the allergıc ırrıtabılıty of the gumea pıg, that ıs, ıts capacıty to react to antıgenıc substances, was ıncreased by treatment wıth trypan blue The technıc employed renders the experıments noncomparable to others

Klınge, ın 1927, studyıng local anaphylaxıs, found that ınflammatıon could be lessened or entırely prevented by the ınjectıon ıntravenously or dırectly ınto the tıssues of trypan blue the day before sensıtızatıon or just before the second ınjectıon of antıgen Protocols were not gıven ın the artıcle, whıch was a short summary of the work done

Summary There ıs no conclusıve evıdence that anaphylactıc shock can be modıfied by treatment wıth trypan blue

Ultra violet light

Giaume, in 1928, concluded that treatment of the serum used for the second injection of antigen with ultra violet light resulted in an inhibition of shock in animals with normal serum, not in those sensitized with irradiated serum In 1 set the 6 controls died, while 12 animals had no shock that received serum which had been irradiated with a Bach lamp of 110 volts, continuous current, 1500 C P , at a distance of 50 cms , for 30 minutes Serum was treated from 30 to 60 minutes before use In another series, 4 controls died and of 4 animals which had been given serum irradiated for 5 minutes, 3 survived moderate shock and 1 died of hemorrhage Four animals given serum which had been treated for 30 minutes had no shock

Urethane

Besredka, in 1908, found that 0 4 gram of urethane prolonged the life of shocked guinea pigs No protocols were given and the number of controls was not stated

Anderson and Schultz, in 1909, as has been discussed under "Adrenalin" gave combined treatments of urethane, chloralhydrate and adrenaline and also in some cases, artificial respiration with oxygen The rôle of the urethane in these experiments cannot be determined, but the results with the treated animals were better than with the controls

Rosenau and Anderson, in 1909, found no definite inhibition of shock by giving sensitized animals 0 9 or 1 0 gram or urethane by mouth 45 or 70 minutes before the intraperitoneal injection of 6 cc of the antigen

Urine

Pfeiffer, in 1911, studying the increased toxicity of urine in anaphylactic shock, carried out a few experiments on the inhibition of shock with urine In one series (Table 33, page 611) guinea pigs were sensitized with normal horse serum and given 2 intraperitoneal injections of toxic, anaphylactic urine, 18 and 19 days after sensitization The second injection of antigen was given 48 hours after the second treatment As compared with the 3 controls, the 2 treated animals were definitely protected

In a similar series (Table 34, page 642), sensitized guinea pigs were given 2 intraperitoneal injections, as in the first series, of 2 cc of toxic urine and it was found that 5 of the 8 treated animals were protected, as compared with the 8 untreated controls No experiments with normal urine were described We therefore have some evidence of the protective effect of urine, but none as to whether this is limited to anaphylactic urine or not

Vagus section

Auer, in 1910, was unable to find that section of the vagus before or after desensitization had any effect upon the production of anaphylactic shock Neither did complete or partial degeneration of the vagus nerve

Auer and Lewis, in 1910, found that section of both vagi had no protective effect upon shock, such as would be expected if the action of the second injection of antigen was upon the medullary centers There were no protocols for this work

Friedberger and Grober, in 1913, believed that they obtained definite protection against 3 lethal doses of antigen by vagotomy Of the 8 untreated controls, 7 died after from 0 23 to 0 35 cc per kilogram of the serum antigen and the 8th animal survived 0 26 cc per kilogram with shock Of the 4 guinea pigs with section of the vagus, 2 had bilateral section One of these died 15 minutes after 3 7 lethal doses of antigen, the lungs on autopsy being a little distended The other had light shock One animal had left vagotomy and died without distension of the lungs 25 minutes after 4 lethal doses of antigen The animal which had right vagotomy had no symptoms from 3 5 lethal doses

Galambos, in 1913, continued the work of Friedberger and Grober He found that of 3 guinea pigs with both vagi cut, 1 died of anaphylaxis after 0 6 cc of antigen, 1 which had 0 4 cc of antigen, was ill, but recovered and another died 30 minutes after 0 2 cc of antigen, with no anaphylactic pathology Of two animals with the right vagus cut, 1 survived 0 2 cc of antigen and the other died from 0 6 cc Of the the controls, 3 untreated animals were killed by 0 12 cc of antigen

Summary Work has been done which shows that vagus section may, in some cases, prevent fatal anaphylactic shock

Vitamine A deficiency

Wedgewood and Grant, in 1924, working with rats, concluded that vitamine A deficiency did not render their animals more sensitive

Vitamin B deficiency

Aberhalden and Wertheimer, in 1922, sensitized pigeons with beef serum and kept them on a diet exclusively of polished rice The second injection of antigen was given upon the appearance of alimentary dystrophy, that is, in about 20 days The 4 dieted animals had much more shock than the controls The technique employed was that of observing temperature changes All of the treated animals died, but only 1 of the controls

Wedgewood and Grant, in 1924, found that if young rats were given a diet deficient in vitamin B, they were predisposed to sensitization, or the effect of sensitization was increased Five rats were kept on a vitamin B deficient diet for 2 weeks or longer during the sensitization period, and died when shocked The authors concluded that vitamin B—either desensitized, prevented sensitization or protected against shock

Vitamin C

Zolog, in 1924, kept guinea pigs on a scorbutic diet for 1 month before sensitization and during sensitization He then found them resistant to 8 times the dose of antigen lethal for undieted controls This dosage of antigen was calculated per 100 grams of weight

Wedgewood and Grant, in 1924, concluded that vitamin C deficiency did not render young rats susceptible to sensitization

Wedgewood, in 1924, kept 5 guinea pigs on a complete diet during 2 weeks of sensitization and found that then 1 cc of a 10 per cent solution of the antigen, egg white, given intraperitoneally, killed all of them In the treated series, 5 guinea pigs were given intraperitoneally 5 cc of sterile, neutralized orange juice daily during sensitization These animals had shock but recovered when given the same amount of antigen as the controls In another group, kept on a scorbutic diet for 16 days before shock, 4 died and 1 recovered from shock

Water

See also Mineral Waters

Besredka, in 1907-c, found that precipitation of the serum antigen with distilled water did not diminish the toxicity

Richet, Brodin and Saint-Girons, in 1919, showed that in 3 dogs, no protection against shock was obtained by diluting the shocking dose of antigenic serum with 9 times its volume of distilled water The amount of antigen may have been too high to allow the determination of small differences

Whey protein

Besredka, in 1908, found that while whey did not sensitize, when it was given intraperitoneally to guinea pigs which had been sensitized with milk, the animals were protected against the second injection of milk, given intracranially He produced anti anaphylaxis with 10 cc of "lait cru," given by rectum or by mouth The number of controls was not stated, 0 1 cc of antigen being the lethal dose

Banzhaf and Steinhardt, in 1910, believed that Besredka had diluted the active protein, not separated it into fractions

Bauer, in 1912, sensitized animals with 1 cc of whole milk, given intraperitoneally and treated them with from 0 5 to 10 cc of whey protein, given intravenously One animal was used for each dosage For shock, 4 cc of casein was given intravenously 1 day after the whey protein injection One of the 2 controls which received 4 cc of casein intravenously recovered after severe shock, and the other died Of the 5 animals treated with different doses of whey protein only the animals receiving the smallest amount of treatment, 0 5 cc died The 2 which had 1 0 and 2 5 cc of whey had severe or moderate shock but recovered Those which had 5 and 10 cc of whey had mild or no shock In another series of experiments, Bauer found that the 5 animals, treated with 0 5 to 20 cc of whey protein intraperitoneally the day before shock, had mild shock upon the injection of 1 cc of casein intravenously The 3 controls died after the same amount of antigen This second series, which was more convincing than the first, because better controlled, seems to offer definite evidence that whey protein inhibits anaphylactic shock with casein in animals sensitized to milk

Reviews In addition to these articles on particular aspects of this problem,

the following reviews on the inhibition of anaphylactic shock may be cited Thomsen, 1917, Kopaczewski, 1920, Widal, Abrami and Vallery-Radot, in 1921, who gave no bibliography, and the short paper by Isaacs in 1929 The problem is also discussed briefly in the more general reviews on anaphylaxis, notably those of Doerr, in 1913, of Kraus, in 1919, of Coca in Tice's Practice of Medicine, of Wells, in 1921, of Doerr, in 1922, of Dale, in 1922, and of Longcope, in 1923

BIBLIOGRAPHY

ABERHALDEN, E AND WERTHEIMER, E Pfluger's Archiv , 1922, cxcvi, 440
ACHARD, C AND FLANDIN, C Comptes rend Soc de biol , 1911, lxxi, 91
AMBERG, S AND KNOX, J H M Jour Amer Med Assoc , 1912-a, lix, 1598
AMBERG, S AND KNOX, J H M Jour Pharmacol and Exper Therap , 1912-b, iii, 223
ANDERSON, J F AND FROST, W H Jour Med Research, 1910, xxiii, 31
ANDERSON, J F AND ROSENAU, M J Jour Med Research, 1908, xix, 41
ANDERSON, J F AND ROSENAU, M J Jour Med Research, 1909, xxii, 1
ANDERSON, J F AND SCHULTZ, W H Proc Soc of Exper Biol and Med , 1909, vii, 32
ANDO, J Zeitschr Immunitat , 1913, xviii, 1
APPELMANS, R Comptes rend Soc de biol , 1922, lxxxvii, 1242
APPELMANS, R Comptes rend Soc de biol , 1923, lxxxviii, 1216
ARGAUD, R AND BILLARD, G Comptes rend Soc de biol , 1911, lxx, 746
ARLOING, F , LANGERON, 1 MILHAUD, AND RICARD Comptes rend Soc de biol , 1923, lxxxix, 1296
ARLOING, F AND VAUTHEY, P Comptes rend Soc de biol , 1921, lxxxiv, 519
ARLOING, F AND VAUTHEY, P Comptes rend Soc de biol , 1922-a, lxxxvi, 687
ARLOING, F AND VAUTHEY, P Comptes rend Soc de biol , 1922-b, lxxxvi, 689
ARLOING, F AND VAUTHEY, P Comptes rend Soc de biol , 1923, lxxxviii, 505
ARMAND-DELILLE, P AND LAUNOY, I Comptes rend Soc de biol 1912, lxxii, 61
ARONSON, H Berl klinische Wochenschr 1912–1, 251
ASCOLI, A Zeitschr Immunitat , 1910, vi, 161
AUER, J Amer Jour of Physiol , 1910-a, xxvi, 439
AUER, J Jour exper Med 1910-b, xii, 638
AUER, J Zeitschr Immunitat , 1912, xii, 235
AUER, J AND LEWIS, P A Jour Amer Med Assoc , 1909, liii, 458
AUER, J AND LEWIS, P A Jour Exper Med 1910, xii, 151
BANZHAF, E J AND FAMULENER, L W Proc Soc Exper Biol and Med , 1908, v, 62
BANZHAF, E J AND FAMULENER, L W Jour Infectious Diseases, 1910, vii, 577
BANZHAF, E J AND STEINHARDT, E Jour Med Research, 1910-a, xxiii, 1
BANZHAF, E J AND STEINHARDT, E Jour Med Research, 1910-b, xxiii, 5
BAUER, J Centralbl f Bakt , 1912, Orig , lxvi, 303
BELIN, M Jour de physiol et de pathol générale, 1911, xiii, 372
BELIN, M Comptes rend Soc de biol , 1913, lxxiv, 173
BELLIN cited by Ferreyrolles
BENJAMIN AND WITZINGER Zeitschr f Kinderheil , 1911, iii, 73
BESREDKA, A Comptes rend Soc de biol , 1907-a, lxii, 1053
BESREDKA, A Annales de l'Inst Pasteur, 1907-b, xxi, 777
BESREDKA, A Annales de l'Inst Pasteur, 1907-c, xxi, 950
BESREDKA, A Annales de l'Inst Pasteur, 1908-a, xxii, 496
BESREDKA, A Comptes rend Soc de biol , 1908-b, lxv, 478

BESREDKA, A. Annales de l'Inst. Pasteur, 1920, xxxiv, 334
BESREDKA, A Anaphylaxis and Anti anaphylaxis and Their Experimental Foundations, English Edition by S Roodhouse Gloyne, William Heinemann Ltd, London, 1919
BESREDKA, A, STRODEL, H, AND JUPILLE, F Zeitschr f Immunität, 1913, xvi, 249
BESSAU, G Centralbl f Bakt, 1911, Orig lx, 637
BESSAU, G, OPITZ H, AND PALUSSE, O Centralbl f Bakt 1914, lxxiv, 162
BIEDL, A AND KRAUS, R Wiener klinische Wochenschr, 1909, xxii, 365
BIEDL, A AND KRAUS, R Wiener klinische Wochenschr, 1910, xviii, 386
BILLARD, G Comptes rend Soc de biol, 1913, lxxiv, 99
BILLARD, G AND BARDÈS, L Comptes rend Soc de biol, 1913, lxxiv, 1320
BILLARD, G AND DAUPEYROUX, R Comptes rend Soc de biol 1913, lxxiv, 1018
BILLARD, G AND GRELLETY, R Comptes rend Soc de biol, 1913, lxxiv, 666
BORNSTEIN Zeitschr Immunitat, 1912, xiv, 605
BRACK, W Zeitschr Immunität, 1921, xxxi, 407
BRODIN, P AND HUCHET, P Comptes rend Soc de l'Acad des Sc, 1921, clxxiii, 865
CAIN, R Klinische Wochenschr 1924, iii², 1857
CALVARY, M Münch med Wochenschr, 1911, lviii, 1442
CARPANI, G Morgagni Archivio, 1920, lxii, 140
CHASSEVANT, A, GAUP, J AND POIROT DELPECH, J Comptes rend Soc de biol, 1913, lxxiv, 679
COCA, A F Tice's Practice of Medicine, Vol I, 138
COLLIER, W A Zeitschr Immunität, 1927, lii, 191
COMBIESCO, D AND BRAUNER R Comptes rend Soc de biol, 1928, xcix, 421
CORPER, H J Jour of Infectious Diseases, 1919, xxv, 248
CORPER, H J, BLACK L T AND MOORE, M Jour of Infectious Diseases, 1922, xxx, 50
DALE, H H Jour Pharmacol and Exper Therap, 1912–13 a, iv, 167
DALE, H H Jour Pharmacol and Exper Therap, 1912–13 b, iv, 517
DALE, H H British Med Jour 1922, i, 45
DALE, H H AND HARTLEY, P Biochem Jour, 1916, x, 408
DALE, H H AND KELLAWAY, C H Philosophical Trans Roy Soc of London, 1923, ccxi B, 273
DAUPEYROUX Hydrologica, 1913, No 6, June, cited by Ferreyrolles
DOERR, R Wiener klinische Wochenschr, 1908, xxi, 415
DOFRR, R Wiener klinische Wochenschr, 1912, xxv¹, 331
DOERR, R Kolle und Wassermann, Handbuch der Pathogenen Mikroorganismen, 1913, II, 1080 Gustav Fischer, Jena.
DOERR, R Ergebnisse d Hyg u Bakt., 1922, v, 78
DUPREZ, C Comptes rend Soc de biol, 1922, lxxxvi, 285
EGGSTEIN, A A Jour Lab and Clin Med, 1921, vi, 555
FERREYROLLES, P Proc Roy Soc of Med, 1919, xii, No 9, Section of Balneology and Climatology, 1
FLEISCHER, M, AND WILHELMJ Zeitschr Immunitat, 1927-a, li, 115
FLEISCHER, M, AND WILHELMJ Zeitschr Immunität, 1927 b, li, 126
FRIEDBERGER, E Zeitschr Immunitat, 1910, iv, 684
FRIEDBERGER, E Zeitschr Immunität, 1911, viii 239
FRIEDBERGER, E Verhandlungen des Kongress für innerer Medizin, Wiesbaden, 1913 a, page 88, (30th Kongress)
FRIEDBERGER, E Zeitschr Immunität, 1913 b, xviii, 280

FRIEDBERGER, E AND GOLDSCHMID, E Zeitschr Immunitat, 1910, vi, 299
FRIEDBERGER, E AND GROBER, A Zeitschr Immunitat, 1913, xix, 429
FRIEDBERGER, E AND HARTOCH, O Zeitschr Immunitat, 1909, iii, 581
FRIEDBERGER, E AND KUMAGAI, T Zeitschr Immunitat, 1913, xix, 445
FRIEDBERGER, E AND LANGER, H Zeitschr Immunitat, 1912, xv, 535
FUJIOKA, N Japan Med World, 1925, v, 319
GALAMBOS, A Zeitschr Immunitat, 1913, xix, 437
GALUP, J Presse Méd, 1920, xxviii, 445
GAY, F P, AND SOUTHARD, E E Jour Med Research, 1908, xix, 1
GIAUME, C Pathologica, 1928, xx, 236
GOBERT, E Comptes rend Soc de biol, 1913, lxxiv, 1240
HANZLIK, P J, BUTT, E M AND STOCKTON, A B Jour Immunol, 1927, xiii, 409
HANZLIK, P J AND KARSNER, H T Jour Pharmacol and Exp Therap, 1920, xiv, 425
HARTOCH, O AND SIRENSKIJ, N Zeitschr Immunitat, 1912, xii, 85
HEILNER, E Zeitschr Biol, 1908, L, 476
HEKTOEN, L AND CORPER, H J Jour Infectious Diseases, 1921, xxviii, 279
HENRIJEAN, F AND KOPACZEWSKI, W Comptes rend Soc de biol, 1925, xcii, 192
HEYDE, M Zentralbl fur Physiologie, 1912, xxvi, 401
HOUSSAY, B -A AND SORDELLI, A Comptes rend Soc de biol 1923, lxxxviii, 354
HYDE, R R American Jour Hyg, 1927, vii, 614
ISAACS, M L Med Bull, Univ of Cincinnati, 1924, ii, 181
ISAACS, M L Proc Soc Exper Biol and Med, 1925, xxiii, 185
ISAACS, M L Arch Pathol, 1928, v, 1928
JOBLING, J W AND PETERSEN, W F Jour Exper Med, 1914, xx, 468
JUNGEBLUTT, C W Proc Soc Exper Biol and Med, 1927–28, xxv, 368
KARSNER, H T AND ECKER, E E Jour Infectious Diseases, 1922, xxx, 333
KARSNER, H T AND ECKER, E E Jour Infectious Diseases, 1924, xxxiv, 636
KARSNER, H T AND NUTT, J B Jour Amer Med Assoc, 1911-a, lvii, 1023
KARSNER, H T AND NUTT, J B Proc Soc Exper Biol and Med, 1910–11-b, viii, 108
KASTLE, J H, HEALY, D J AND BUCKNER, G D Jour Infectious Diseases, 1913, xii, 127
KELLAWAY, C H AND COWELL, S J British Jour Exper Pathol, 1922, iii, 268
KÉPINOW, L Comptes rend Soc de biol, 1922-a, lxxxvii, 327
KÉPINOW, L Comptes rend Soc de biol, 1922-b, lxxxvii, 409
KÉPINOW, L Comptes rend Soc de biol, 1922-c, lxxxvii, 494
KÉPINOW, L Comptes rend Soc de biol, 1923, lxxxviii, 846
KÉPINOW, L, AND LANZENBERG, A Comptes rend Soc de biol, 1922, lxxxvi, 906
KÉPINOW, L AND LANZENBERG, A Comptes rend Soc de biol, 1923, lxxxviii, 165
KEYES, P AND STRAUSER, E R Jour Immunol, 1926, xii, 419
KLINGE, F Deutsche med Wochenschr, 1927, liii, 1903
KLOPSTOCK, A Klinische Wochenschr, 1925, iv, 313
KONSTANTOFF, S Comptes rend Soc de biol, 1912, lxxii, 263
KOPACZEWSKI, W Annales de Méd, 1920, viii, 291
KOPACZEWSKI, W AND ROFFO, A H Comptes rend Soc de biol, 1920, lxxxiii, 837
KOPACZEWSKI, W, ROFFO, A H AND ROFFO, H L Comptes rend de l'Acad des Sciences, 1920, clxx, 1409
KOPACZEWSKI, W AND VAHRAM, A Comptes rend de l'Acad des Sciences, 1919, clxix, 250

KRAUS, R Revista del Instituo Bacteriologico del Departmento Nacional de Hygiene, 1919, II, 1
KUMAGAI, T AND ODAIRA Zeitschr Immunität, 1912, xiv, 391
LANZENBERG, A AND KÉPINOW, L Comptes rend Soc de biol, 1922, lxxxvi, 204
LARSON, N P, HAIGH, A V R, ALEXANDER, H L AND PADDOCK, R Jour Immunol, 1923, viii, 409
LASSABLIÈRE, P AND RICHET, C Comptes rend Soc de biol, 1911, lxx, 637
LAUNOY, L AND TALGUE, A Comptes rend Soc de biol, 1922, lxxxvi, 102
LESNÉ, E AND DREYFUS, L Comptes rend Soc de biol, 1911, lxx, 136
LEVY SOLAL AND ZANCK, A Comptes rend Soc de biol, 1923, lxxxix, 503
LEWIS, J H Jour Infectious Diseases, 1915, xvii, 241
LEWIS, P A AND LOOMIS, D Jour Exper Med, 1926, xliii, 263
LOEFFLER, F C Zeitschr Immunität, 1910, viii, 129
LOEWIT, M Archiv für Exper Pathologie, 1911, lxv, 337
LONGCOPE, W T Physiolog Review, 1923, iii, 240
LUMIÈRE, A AND CHEVROTIER, J Comptes rend de l'Acad des Sciences, 1920, clxxi, 741
LUMIÈRE, A AND COUTURIER, H Comptes rend de l'Acad des Sciences, 1921 a, clxxii, 294
LUMIÈRE, A AND COUTURIER, H Comptes rend de l'Acad des Sciences, 1921 b, clxxii, 772
LUMIÈRE, A AND COUTURIER, H Comptes rend de l'Acad des Sciences, 1921-c, clxxiii, 800
LUMIÈRE, A AND COUTURIER, H Comptes rend de l'Acad des Sciences, 1922, clxxiv, 495
LUMIÈRE, A AND COUTURIER, H Comptes rend de l'Acad des Sciences, 1923, clxxvi, 1019
LUMIÈRE, A AND ENSELME, J Comptes rend de l'Acad des Sciences, 1926, clxxxiii, 577
LURÀ, A Zeitschr Immunität, 1912, xiv, 403
MAKAROWA, J AND ZEISS, H Zeitschr Immunität., 1926, xlvii, 110
MANWARING Zeitschr Immunität, 1910, viii, 1
MARTIN, L AND HILL, J H Bull Johns Hopkins Hosp, 1930, xlvi, 232
MASSINI, R Zeitschr Immunität, 1918, xxvii, 213
MICHELAZZI, L Pathologica, 1927, xix, 527
MITA, S Zeitschr Immunität, 1911, xi, 501
MOLDOVAN, J AND ZOLOG, M Comptes rend Soc de biol, 1923 a, lxxxix, 1239
MOLDOVAN, J AND ZOLOG, M Comptes rend Soc de biol, 1923 b, lxxxix, 1242
MOLDOVAN, J AND ZOLOG, M Comptes rend Soc de biol, 1925, xcii, 720
MOUGEOT, A Comptes rend Soc de biol, 1919, lxxxii, 191
NECHKOVITCH Comptes rend Soc de biol, 1924, xci, 809
NETTER, A Comptes rend Soc de biol, 1906-a, lx, 279
NETTER, A Comptes rend Soc de biol, 1906-b, lx, 281
PARHON, C I AND BALLIF, J Comp rend Soc de biol, 1923 a, lxxxviii, 544
PARHON, C I AND BALLIF, L Comp rend Soc de biol, 1923 b, lxxxix, 1063
PELZ, M D, JACKSON, D E Jour Pharmacol and Exper Therap, 1918, xi, 173
PERRIN, M AND ABEL, E Comptes rend Soc de biol, 1927, xcvii, 1627
PETERSEN, W F, JAFFE R H, LEVINSON, S A AND HUGHES, T P Jour Immunol, 1923, viii, 367
PFEIFFER H Zeitschr Immunität, 1911, x, 550
PFEIFFER, H AND JARISCH, A Zeitschr Immunitat, 1913, xvi, 38

PFEIFFER, H AND MITA, S Zeitschr Immunitat, 1910, iv, 410
PICO, C -E Comptes rend Soc de biol, 1924, xci, 1049
PIERRET AND CRAMPON Comptes rend Soc de biol, 1923, lxxxix, 1282
PISTOCCHI, G Pathologica Revista Quindicinal, 1920, xii, 239
REED, C L AND LAMSON, R W Jour Immunol, 1927, xiii, 433
REYNALLS, J DURAN Revue espagnole d'Obstetrique et de Gynécologie, 1920, No 58, 458, cited by Lumière and Couturier, 1922
RICHET, C, BRODIN, P AND SAINT-GIRONS, F Comptes rend de L'Acad des Sciences, 1919, clxix, 9
RICHET, C, BRODIN, P AND SAINT-GIRONS, F Revue de Med, 1920, xxxvii, 7
RITZ, H Zeitschr Immunitat, 1912, xii, 644
ROSENAU, M J AND ANDERSON, J F Hygienic Lab Bulletin, No 29, 1906, April
ROSENAU, M J AND ANDERSON, J F Hygienic Lab Bulletin No 45, 1908, June
ROSENAU, M J AND ANDERSON, J F Hygienic Lab Bulletin, No 50, 1909, April
RUSZNYÁK, S Zeitschr Immunitat, 1920, xxx, 1
RUSZYNÁK, S AND KORÁNYI, A Klinische Wochenschr, 1927–2, vi, 1332
SALVAGNINI, G Bullettino della Società Medico-Chirurgica di Pavia, 1927, ii, (new series), 483
SAVINI, E AND SAVINI, T Comptes rend Soc de biol, 1915, lxxviii, 198
SAVINI, E Comptes rend Soc de biol, 1923, lxxxviii, 235
SCHIFF, F Zeitschr Immunitat, 1915, xxiii, 61
SCHMIDT, H Zeitschr Immunitat, 1926, xlv, 496
SCHNEIDER, E Klinische Wochenschr, 1927, vi, 1037
SCHURER, J AND STRASMANN, R Zeitschr Immunitat, 1912, xii, 143
SELIGMANN, E Zeitschr Immunitat, 1912, xiv, 419
SICARD AND PAROF Bull et Mem Soc med des Hop de Paris, 1921-a, xlv, 60
SICARD AND PAROF Bull et Mem Soc med des Hop de Paris, 1921-b, xlv, 229
SIMITCH, TICH-V Comptes rend Soc de biol, 1926, xciv, 23
SMITH, M I Jour Immunol, 1920, v, 239
STERN, W AND REISS, M Zeitschr gesammt exper Med, 1922, xxix, 388
STOLAND, O O AND SHERWOOD, N P Jour Immunol, 1923, viii, 91
SUAREZ, E Annales de l'Inst Pasteur, 1928, cliii, 877
SUAREZ, E AND SCHALTER, W Annales de l'Inst Pasteur, 1928-a, xlii, 1447
SUAREZ, E AND SCHAEFER, W Annales de l'Inst Pasteur, 1928-b, xlii, 1458
SURÁNYI, L AND JARNO, L Zeitschr Immunitat, 1928, lvi, 303
SZYMANOWSKY, Z Zeitschr Immunitat, 1912, xiv, 381
TEALE, F H AND BACH, E Proc Roy Soc of Med, 1919–20, xiii, Part III, Section of Pathology, 5
THOMSEN, O Zeitschr Immunitat, 1917, xxvi, 213
VAN DE CARR, F R, LYONS, W R AND WILLIAMS, O B Jour Immunol, 1928, xv, 355
VOEGTLIN, C AND BERNHEIM, B M Jour Pharmacol and Exper Therap, 1910–1911, ii, 507
VON DUNGERN AND HIRSCHFELD Zeitschr Immunitat, 1911, xi, 557
VON HEINRICH, H Centralbl Bakt, Orig, 1913, lxx, 421
VON PIRQUET, C Deutsche med Wochenschr, 1908, 1297
WEDGEWOOD, P E Med Bull, Univ of Cincinnati, 1924, 178
WEDGEWOOD, P E AND GRANT, A H Med Bull, Univ of Cincinnati, 1924, 172
WEIL, R Jour Med Research, 1913, xxviii, 243

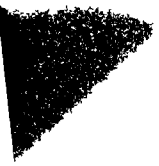
WEIL, R Zeitschr Immunität, 1914, xx, 199
WEIL, R AND COCA, A F Zeitschr Immunität, 1913, xvii, 141
WELLS, H G Physiolog Reviews, 1921, i, 44
WELLS, H G AND OSBORNE, T B Jour Infectious Diseases, 1913, xii, 341
WIDAL, F, ABRAMI P AND VALLERY RADOT, P Presse Med, 1921, xxix, 781
WIECHMANN, E AND KOCH, F Arch f exper Pathol u Pharmakol, 1928, cxxxii, 911
WILLIAMS, O B AND VAN DE CARR, I R Proc Soc Exper Biol and Med, 1927, xxiv, 798
ZINSSER, H, LIEB, C C AND DWYER, J G Proc Soc Exper Biol and Med, 1914–15, xii, 205
ZOLOG, M Comptes rend Soc de biol, 1924, xci, 215
ZUNZ, E AND LA BARRE, J Comptes rend Soc de biol, 1923, lxxxviii, 645
ZUNZ, F AND LA BARRE, J Comptes rend Soc de biol, 1924, xci, 132
ZUNZ, E AND VAN GEERTRUYDEN BERNARD Comptes rend Soc de biol, 1921, lxxxiv, 287

PFEIFFER, H AND MITA, S Zeitschr Immunitat , 1910, iv, 410
PICO, C -E Comptes rend Soc de biol , 1924, xci, 1049
PIERRET AND CRAMPON Comptes rend Soc de biol , 1923, lxxxix, 1282
PISTOCCHI, G Pathologica Revista Quindicinal, 1920, xii, 239
REED, C L AND LAMSON, R W Jour Immunol , 1927, xiii, 433
REYNALLS, J DURAN Revue espagnole d'Obstetrique et de Gynécologie, 1920, No 58, 458, cited by Lumière and Couturier, 1922
RICHET, C , BRODIN, P AND SAINT-GIRONS, F Comptes rend de L'Acad des Sciences, 1919, clxix, 9
RICHET, C , BRODIN, P AND SAINT-GIRONS, F Revue de Med , 1920, xxxvii, 7
RITZ, H Zeitschr Immunitat , 1912, xii, 644
ROSENAU, M J AND ANDERSON, J F Hygienic Lab Bulletin, No 29, 1906, April
ROSENAU, M J AND ANDERSON, J F Hygienic Lab Bulletin No 45, 1908, June
ROSENAU, M J AND ANDERSON, J F Hygienic Lab Bulletin, No 50, 1909, April
RUSZNYÁK, S Zeitschr Immunitat , 1920, xxx, 1
RUSZYNÁK, S AND KORÁNYI, A Klinische Wochenschr , 1927–2, vi, 1332
SALVAGNINI, G Bullettino della Società Medico-Chirurgica di Pavia, 1927, ii, (new series), 483
SAVINI, E AND SAVINI, T Comptes rend Soc de biol , 1915, lxxviii, 198
SAVINI, E Comptes rend Soc de biol , 1923, lxxxviii, 235
SCHIFF, F Zeitschr Immunitat , 1915, xxiii, 61
SCHMIDT, H Zeitschr Immunitat , 1926, xlv, 496
SCHNEIDER, E Klinische Wochenschr , 1927, vi, 1037
SCHURER, J AND STRASMANN, R Zeitschr Immunitat , 1912, xii, 143
SELIGMANN, E Zeitschr Immunitat , 1912, xiv, 419
SICARD AND PAROF Bull et Mem Soc med des Hop de Paris, 1921-a, xlv, 60
SICARD AND PAROF Bull et Mem Soc med des Hop de Paris, 1921-b, xlv, 229
SIMITCH, TICH-V Comptes rend Soc de biol , 1926, xciv, 23
SMITH, M I Jour Immunol , 1920, v, 239
STERN, W AND REISS, M Zeitschr gesammt exper Med , 1922, xxix, 388
STOLAND, O O AND SHERWOOD, N P Jour Immunol , 1923, viii, 91
SUAREZ, E Annales de l'Inst Pasteur, 1928, cli, 877
SUAREZ, E AND SCHAEFER, W Annales de l'Inst Pasteur, 1928-a, xlii, 1447
SUAREZ, E AND SCHAEFER, W Annales de l'Inst Pasteur, 1928-b, xlii, 1458
SURÁNYI, L AND JARNO, L Zeitschr Immunitat , 1928, lvi, 303
SZYMANOWSKY, Z Zeitschr Immunitat , 1912, xiv, 381
TEALE, F H AND BACH, E Proc Roy Soc of Med , 1919–20, xiii, Part III, Section of Pathology, 5
THOMSEN, O Zeitschr Immunitat , 1917, xxvi, 213
VAN DE CARR, F R , LYONS, W R AND WILLIAMS, O B Jour Immunol , 1928, xv, 355
VOEGTLIN, C AND BERNHEIM, B M Jour Pharmacol and Exper Therap , 1910–1911, ii, 507
VON DUNGERN AND HIRSCHFELD Zeitschr Immunitat , 1911, xi, 557
VON HEINRICH, H Centralbl Bakt , Orig , 1913, lxx, 421
VON PIRQUET, C Deutsche med Wochenschr , 1908, 1297
WEDGEWOOD, P E Med Bull , Univ of Cincinnati, 1924, 178
WEDGEWOOD, P E AND GRANT, A H Med Bull , Univ of Cincinnati, 1924, 172
WEIL, R Jour Med Research, 1913, xxviii, 243

WEIL, R Zeitschr Immunität, 1914, xx, 199
WEIL, R AND COCA, A F Zeitschr Immunität, 1913, xvii, 141
WELLS, H G Physiolog Reviews, 1921, i, 44
WELLS, H G AND OSBORNE, T B Jour Infectious Diseases, 1913, xii, 341
WIDAL, F, ABRAMI P AND VALLERY RADOT, P Presse Med, 1921, xxix, 781
WIECHMANN, E AND KOCH, F Arch f exper Pathol u Pharmakol, 1928, cxxxii, 911
WILLIAMS, O B AND VAN DE CARR, F R Proc Soc Exper Biol and Med, 1927, xxiv, 798
ZINSSER, H, LIEB, C C AND DWYER, J G Proc Soc Exper Biol and Med, 1914–15, xii, 205
ZOLOG, M Comptes rend Soc de biol, 1924, xci, 215
ZUNZ, E AND LA BARRE, J Comptes rend Soc de biol, 1923, lxxxviii, 645
ZUNZ, E AND LA BARRE, J Comptes rend Soc de biol, 1924, xci, 132
ZUNZ, E AND VAN GEERTRUYDEN BERNARD Comptes rend Soc de biol, 1921, lxxxiv, 287

PFEIFFER, H AND MITA, S Zeitschr Immunitat, 1910, iv, 410
PICO, C -E Comptes rend Soc de biol, 1924, xci, 1049
PIERRET AND CRAMPON Comptes rend Soc de biol, 1923, lxxxix, 1282
PISTOCCHI, G Pathologica Revista Quindicinal, 1920, xii, 239
REED, C L AND LAMSON, R W Jour Immunol, 1927, xiii, 433
REYNALLS, J DURAN Revue espagnole d'Obstetrique et de Gynécologie, 1920, No 58, 458, cited by Lumière and Couturier, 1922
RICHET, C, BRODIN, P AND SAINT-GIRONS, F Comptes rend de L'Acad des Sciences, 1919, clxix, 9
RICHET, C, BRODIN, P AND SAINT-GIRONS, F Revue de Med, 1920, xxxvii, 7
RITZ, H Zeitschr Immunitat, 1912, xii, 644
ROSENAU, M J AND ANDERSON, J F Hygienic Lab Bulletin, No 29, 1906, April
ROSENAU, M J AND ANDERSON, J F Hygienic Lab Bulletin No 45, 1908, June
ROSENAU, M J AND ANDERSON, J F Hygienic Lab Bulletin, No 50, 1909, April
RUSZNYÁK, S Zeitschr Immunitat, 1920, xxx, 1
RUSZYNÁK, S AND KORÁNYI, A Klinische Wochenschr, 1927–2, vi, 1332
SALVAGNINI, G Bullettino della Società Medico-Chirurgica di Pavia, 1927, ii, (new series), 483
SAVINI, E AND SAVINI, T Comptes rend Soc de biol, 1915, lxxviii, 198
SAVINI, E Comptes rend Soc de biol, 1923, lxxxviii, 235
SCHIFF, F Zeitschr Immunitat, 1915, xxiii, 61
SCHMIDT, H Zeitschr Immunitat, 1926, xlv, 496
SCHNEIDER, E Klinische Wochenschr, 1927, vi, 1037
SCHURER, J AND STRASMANN, R Zeitschr Immunitat, 1912, xii, 143
SELIGMANN, E Zeitschr Immunitat, 1912, xiv, 419
SICARD AND PAROF Bull et Mem Soc med des Hop de Paris, 1921-a, xlv, 60
SICARD AND PAROF Bull et Mem Soc med des Hop de Paris, 1921-b, xlv, 229
SIMITCH, TICH-V Comptes rend Soc de biol, 1926, xciv, 23
SMITH, M I Jour Immunol, 1920, v, 239
STERN, W AND REISS, M Zeitschr gesammt exper Med, 1922, xxix, 388
STOLAND, O O AND SHERWOOD, N P Jour Immunol, 1923, viii, 91
SUAREZ, E Annales de l'Inst Pasteur, 1928, clii, 877
SUAREZ, E AND SCHAEFER, W Annales de l'Inst Pasteur, 1928-a, xlii, 1447
SUAREZ, E AND SCHAEFER, W Annales de l'Inst Pasteur, 1928-b, xlii, 1458
SURÁNYI, L AND JARNO, L Zeitschr Immunitat, 1928, lvi, 303
SZYMANOWSKI, Z Zeitschr Immunitat, 1912, xiv, 381
TEALE, F H AND BACH, E Proc Roy Soc of Med, 1919–20, xiii, Part III, Section of Pathology, 5
THOMSEN, O Zeitschr Immunitat, 1917, xxvi, 213
VAN DE CARR, F R, LYONS, W R AND WILLIAMS, O B Jour Immunol, 1928, xv, 355
VOEGTLIN, C AND BERNHEIM, B M Jour Pharmacol and Exper Therap, 1910–1911, ii, 507
VON DUNGERN AND HIRSCHFELD Zeitschr Immunitat, 1911, xi, 557
VON HEINRICH, H Centralbl Bakt, Orig, 1913, lxx, 421
VON PIRQUET, C Deutsche med Wochenschr, 1908, 1297
WEDGEWOOD, P E Med Bull, Univ of Cincinnati, 1924, 178
WEDGEWOOD, P E AND GRANT, A H Med Bull, Univ of Cincinnati, 1924, 172
WEIL, R Jour Med Research, 1913, xxviii, 243

WEIL, R Zeitschr Immunität, 1914, xx, 199
WEIL, R AND COCA, A F Zeitschr Immunität, 1913, xvii, 141
WELLS, H G Physiolog Reviews, 1921, i, 44
WELLS, H G AND OSBORNE, T B Jour Infectious Diseases, 1913, xii, 341
WIDAL, F, ABRAMI P AND VALLERY RADOT, P Presse Med, 1921, xxix, 781
WIECHMANN, E AND KOCH, F Arch f exper Pathol u Pharmakol, 1928, cxxxii, 911
WILLIAMS, O B AND VAN DE CARR, F R Proc Soc Exper Biol and Med, 1927, xxiv, 798
ZINSSER, H, IEB, C C AND DWYER, J G Proc Soc Exper Biol and Med, 1914–15, xii, 205
ZOLOG, M Comptes rend Soc de biol, 1924, xci, 215
ZUNZ, E AND LA BARRE, J Comptes rend Soc de biol, 1923, lxxxviii, 645
ZUNZ, F AND LA BARRE, J Comptes rend Soc de biol, 1924, xci, 132
ZUNZ, E AND VAN GEERTRUYDEN BERNARD Comptes rend Soc de biol., 1921, lxxxiv, 287



THE CONTROL OF TONUS AFTER INJURIES TO THE BRAIN OR SPINAL CORD OF MAN

ORTHELLO R LANGWORTHY

Sub-department of Neurology, the Johns Hopkins University

Some years ago the author published a review dealing with the morphology and physiology of the postural reflex (Langworthy, 1928) By the postural reflex is meant the precise control of the pattern of tonus that makes it possible for the organism to counteract the force of gravity and to balance upon the legs In this review experimental data concerning the physiology of the postural reflex was presented and it was shown that this information was conflicting at almost every point One very illuminating result of this experimental work, however, makes the whole subject more comprehensible Tonus is not controlled or mediated by one part or another of the nervous system but is a function of the entire brain and cord acting together, a function of the total individual (Cobb, 1925) Under these conditions it is difficult to evaluate the part played by different structures in the brain in this perfect control Yet this is exactly the thing that the physiologist has wished to do The question always arises in physiology as to the way in which results obtained from study of the dismembered organism correspond to the pattern as seen in the intact individual

Walshe (1929) has recently emphasized the fact that great care must be used in studying a problem such as tonus from the standpoint of phylogeny and applying the results obtained in the experimental animal to the problem of tonus in man This has also been pointed out by the present author when he suggested, for example, that Rademaker's findings in the rabbit did not apply in their entirety even to other laboratory mammals

It must be clearly understood that, in the course of phylogenetic development, now one portion of the central nervous system and now another has gained a dominant control over the tonic reflex From

time to time under the stimulus of increased peripheral or central connections, portions of the brain have undergone enormous increase in size and from these areas new efferent pathways have developed, discharging their impulses either directly or indirectly upon the cells of the final common motor path In phylogeny now one efferent pathway and now another has assumed a dominant control over the tonic and phasic contractions of striated muscle In lower vetebrates, local reflex arcs in the spinal cord are capable of controlling the postural reflex in a fairly normal manner without the aid of impulses from the brain But in the ascending phylogenetic scale, the final common path has come to be more and more under the domination of higher cerebral centres The first important efferent pathway from the brain arose from scattered cells in the reticular formation of the brain stem, the vestibulo-spinal and then the rubro-spinal traits were developed later. The efferent connections of the corpora striata show important phylogenetic variations as Wilson (1914) has pointed out But in mammals these nuclei make only indirect connections with the final common path by way of the red nucleus, substantia nigra and thalamus Finally, the cerebral motor centres have undergone progressive differentiation, exerting their influence directly or through the cerebellum Studies of the postural reflex, then, must take into consideration the relative functional importance of these efferent pathways in the particular animal studied experimentally Among many well-known examples of the importance of this principle one might mention the wide variations in the behavior of man compared with the common laboratory mammals after injury to the cortico-efferent tracts or after complete transection of the spinal cord

Since there exist these differences in the functional importance of cerebral centres in different mammals it seems important to gauge their relative importance in one animal An opportunity to study the pathways controlling tonus in man is made possible by the recent investigations particularly of English clinical neurologists There are, for example, the observations of Riddoch on spinal man (1917), of Holmes on cerebellar injuries (1917 and 1918), of Wilson (1914) on disorders of the basal ganglia and Walshe s (1929) interpretation of hemiplegia on the basis of modern physiology

In order to correlate this material, tonus will be considered in the

present paper under the following headings the control of tonus through a local reflex arc in a single segment of the cord, control by intersegmental spinal reflexes, by the brain stem, by the cerebellum, by the corpus striatum and by the cerebral cortex Although it would be best to consider each of these portions of the nervous system in terms of reflex arcs, controlling the primary reflex arc through the muscle, it is extremely helpful in this general discussion to begin by presenting Sherrington's thesis of the final common path

It must, of course, not be forgotten that it is idle to speak of motor pathways and influences mediated by them without keeping the idea of the reflex arc clearly in mind The motor responses are in every case governed by sensory stimuli which activate the motor side of the reflex pathway Inasmuch as the sensory and correlation pathways are so difficult to study anatomically and physiologically, it is perhaps permissible to simplify this extremely difficult problem of tonus as much as possible and focus attention on the motor side of the reflex pathway This has ever been the tendency of clinical and non-clinical investigators

THE FINAL COMMON PATH

Sherrington (1906) suggested that all the motor cells in the anterior gray columns of the spinal cord and all the motor cells of the cranial nerve nuclei be grouped together and called the final common path since these neurones form the only pathway by which stimuli from central nervous system may exert an influence upon the tone and contraction of muscle or the activity of the glandular structures of the body It makes no difference how many impulses enter the nervous system, the only way they can produce a response is through the final common path

Herrick and Coghill (1915) have given very interesting suggestions concerning the phylogeny of the final common path and have pointed out that in the course of development there has been a marked and progressive development in the motor activity possible They compare the central nervous system to a funnel in which the sensory impulses are poured in at the top and the response through the final common path forms the outlet In amphibia, for example, large numbers and types of sensory responses enter the nervous system but the final

time to time under the stimulus of increased peripheral or central connections, portions of the brain have undergone enormous increase in size and from these areas new efferent pathways have developed, discharging their impulses either directly or indirectly upon the cells of the final common motor path In phylogeny now one efferent pathway and now another has assumed a dominant control over the tonic and phasic contractions of striated muscle In lower vetebrates, local reflex arcs in the spinal cord are capable of controlling the postural reflex in a fairly normal manner without the aid of impulses from the brain But in the ascending phylogenetic scale, the final common path has come to be more and more under the domination of higher cerebral centres The first important efferent pathway from the brain arose from scattered cells in the reticular formation of the brain stem, the vestibulo-spinal and then the rubro-spinal traits were developed later The efferent connections of the corpora striata show important phylogenetic variations as Wilson (1914) has pointed out But in mammals these nuclei make only indirect connections with the final common path by way of the red nucleus, substantia nigra and thalamus Finally, the cerebral motor centres have undergone progressive differentiation, exerting their influence directly or through the cerebellum Studies of the postural reflex, then, must take into consideration the relative functional importance of these efferent pathways in the particular animal studied experimentally Among many well-known examples of the importance of this principle one might mention the wide variations in the behavior of man compared with the common laboratory mammals after injury to the cortico-efferent tracts or after complete transection of the spinal cord

Since there exist these differences in the functional importance of cerebral centres in different mammals it seems important to gauge their relative importance in one animal An opportunity to study the pathways controlling tonus in man is made possible by the recent investigations particularly of English clinical neurologists There are, for example, the observations of Riddoch on spinal man (1917), of Holmes on cerebellar injuries (1917 and 1918), of Wilson (1914) on disorders of the basal ganglia and Walshe's (1929) interpretation of hemiplegia on the basis of modern physiology

In order to correlate this material, tonus will be considered in the

ent paper under the following headings the control of tonus ugh a local reflex arc in a single segment of the cord, control by rsegmental spinal reflexes, by the brain stem, by the cerebellum, he corpus striatum and by the cerebral cortex Although it would best to consider each of these portions of the nervous system in ns of reflex arcs, controlling the primary reflex arc through the cle, it is extremely helpful in this general discussion to begin by enting Sherrington's thesis of the final common path

t must, of course, not be forgotten that it is idle to speak of motor hways and influences mediated by them without keeping the idea he reflex arc clearly in mind The motor responses are in every governed by sensory stimuli which activate the motor side of the ex pathway Inasmuch as the sensory and correlation pathways so difficult to study anatomically and physiologically, it is perhaps missible to simplify this extremely difficult problem of tonus as ch as possible and focus attention on the motor side of the reflex hway This has ever been the tendency of clinical and non-clin- investigators

THE FINAL COMMON PATH

Sherrington (1906) suggested that all the motor cells in the anterior y columns of the spinal cord and all the motor cells of the cranial ve nuclei be grouped together and called the final common path ce these neurones form the only pathway by which stimuli from ntral nervous system may exert an influence upon the tone and ntraction of muscle or the activity of the glandular structures of the dy It makes no difference how many impulses enter the nervous stem, the only way they can produce a response is through the final mmon path

Herrick and Coghill (1915) have given very interesting suggestions ncerning the phylogeny of the final common path and have pointed t that in the course of development there has been a marked and ogressive development in the motor activity possible They com- re the central nervous system to a funnel in which the sensory im- lses are poured in at the top and the response through the final com- on path forms the outlet In amphibia, for example, large numbers d types of sensory responses enter the nervous system but the final

common path is little differentiated, the one response of a tadpole to nocuous stimulation consists in swimming In higher forms the sensory stimuli entering the nervous system are perhaps no more numerous or diversified but the possible motor responses have increased enormously in number

The final common path consists obviously both of somatic motor and autonomic cells Several years ago it was suggested that the tonus of striated musculature was mediated through the autonomic nervous system Many further studies have shown that this is not true indeed it is doubtful whether autonomic fibers end upon striated muscle fibers (Hines and Tower, 1928) It, therefore, is clear that the somatic motor neurones control both the tone and contraction of the striated musculature of the body

It is possible to group in a rough way the types of impulses that act upon one anterior horn cell in the cord that may be taken to typify the final common path In the first place it receives influences from sensory fibers entering the same segment of the cord in which it lies It also receives impulses from other segments of the cord The pathways from the brain are reticulo-spinal, vestibulo-spinal, medial longitudinal fasciculus, rubro-spinal, tecto-spinal and cortico-spinal There may be others but recent work has suggested that even the autonomic component of the final common path is correlated and controlled by impulses through these same well known pathways (Langworthy and Richter, 1930) Perhaps a few suggestions concerning the morphology of these pathways may be given in this place

1 Reticulo-spinal tract Throughout the reticular formation of the brain stem from the lower end of the medulla to the upper end of the midbrain are scattered motor cells These cells give rise to a diffuse pathway which travels down into the spinal cord. The pathway is old phylogenetically and probably was the first pathway from the brain to influence the anterior horn cells It is still probably tremendously important from the standpoint of tone for it is very likely that many of the efferent impulses from the corpus striatum and cerebellum are relayed along this route The fibers are both crossed and uncrossed

2 Vestibulo-spinal tract The vestibulo-spinal is also an old pathway from the standpoint of phylogeny and an extremely prominent

one in controlling the pattern of tonus in connection with vestibular influences It arises from the cells of a distinct portion of the vestibular nucleus called Deiter's nucleus Around these cells end the primary vestibular neurones The cells, however, do not have the structure of other sensory neurones of the second order but resemble motor cells The vestibulo spinal pathway is an uncrossed one Vestibular fibers also cross in the midline and run caudally in the medial longitudinal fasciculus

3 Medial longitudinal fasciculus The medial longitudinal fasciculus is a complex pathway consisting of many groups of fibers (Langworthy, 1929) It has been mentioned that fibers from cells in the vestibular nucleus cross in the midline and travel caudal to influence the cells of the final common path Vestibular fibers also run in a cephalic direction and place the cells of the extraocular nuclei under vestibular influence It also contains fibers that correlate the activity of all the cranial nuclei in the brain stem

4 Rubro spinal tract The rubro spinal tract arises from the large cells at the caudal end of the red nucleus It is said to be relatively small in man The fibers cross the midline The red nucleus receives fibers from the opposite hemisphere of the cerebellum and from the globus pallidus, the place of origin of the efferent pathway from the corpus striatum Its part in the control of tonic patterns is great but never has been adequately defined

The red nucleus in lower mammals consists in the main of the group of large motor cells giving rise to the rubro-spinal tract In higher forms a group of small cells have developed cephalic to the large cells These cells give rise to axones which end around the cells of the reticular formation It has been suggested that the large-celled portion received impulses from nuclei globosus and emboliformis of the cerebellum, the small celled portion from the dentate nucleus In man the small celled portion is very large and the large-celled portion at least relatively diminished in size Since the small cells give rise to fibers ending around the motor cells of the reticular formation, their influence upon the cells of the final common path utilizes an indirect pathway, the morphology of which is not clearly understood

5 Tecto-spinal tract The tecto spinal tract arises from large cells

in the deeper cell layers of the optic colliculi The fibers cross in the midline and run caudally just ventral to the medial longitudinal fasciculi and lateral to the raphe, to influence the cells of the final common path These cells must influence the pattern of tonus in relation to stimuli from the visual apparatus

6 Cortico-spinal tract The cortico-spinal or pyramidal tract is of great importance in man The giant motor cells or Betz cells of the anterior central gyrus give rise to the fibers This pathway is, in general, the agency for the production of volitional quick oscillating movements of the extremities

7 Fronto-pontine and temporo-pontine tracts It is believed that the fronto-pontine pathway arises from cells just anterior to the dorsal portion of the anterior central area The exact region from which the temporo-pontine pathway arises is not yet clearly understood These pathways end around cells in the pontine nuclei and exert their influence through the cerebellar hemispheres The fronto-pontine and temporo-pontine fibers probably exert a normal inhibitory effect over muscle tonus and inhibit the tonus of the opposing muscles when the cortico-spinal pathway initiates precise quick movements The physiology of these pathways from the cerebral cortex will be discussed in detail in a later portion of this paper

THE CONTROL OF TONUS BY AN INDIVIDUAL SEGMENT OF THE CORD

With this hypothesis of the final common path and the impulses which play upon it clearly in mind the question of tonus must be considered in terms of reflex arcs involving different portions of the nervous system The attention however may always be focused on the anterior horn cells since they represent the final portion of each of the reflex arcs

Naturally there is little information concerning the physiology of the individual spinal segment in man and the data here are experimental Sherrington showed that the tonus of the striated musculature was primarily dependent upon sensory impulses from the muscles themselves The proprioceptive fiber from the muscle enters the cord through the posterior root and immediately establishes reflex connections with the anterior horn cell The adequate stimulus for the sensory endings in the muscle consists of stretching, in other words, tonus is fundamentally a stretch reflex

Sensory impulses from the cutaneous surface of the segment have very little influence upon the tonic reflex It was shown however by Sherrington (1906) that stimulation of nerve trunks, such as the sciatic, produced either augmentation or inhibition of the tonus Denny-Brown (1929) has suggested that the two types of sensory endings in the musculature, the tendinous endings and neuromuscular spindles, influence tonus in different ways When the muscle is stretched, the neuro-tendinous endings are first stimulated and send impulses into the segment that increase the tonus If the stretch is continued the neuromuscular spindles that require a higher threshold stimulus influence the activity of the cord in the direction of inhibition If this is true it is an important explanation of certain of the qualities of tonus in the hemiplegic which will be discussed later

Walshe (1929) has been able to show that the hypertonus present in the musculature of man under pathological conditions is also dependent on influences from the proprioceptive endings in the muscle If the proper amount of one per cent novocaine is injected into a hypertonic muscle the sensory nerve endings may be paralyzed and the motor endings unaffected Under these conditions the increased tonus of the muscle is lost but voluntary power retained

If tonus is thought of as controlled by an isolated segment of the cord, the tonus is a property of both the flexor and extensor muscles With certain exceptions that may be disregarded, tone is not a pattern at this level but a property of all striated musculature dependent on afferent impulses from the muscles themselves acting on the anterior horn cells whose axones influence the muscles When several segments of the cord are acting together and many impulses are influencing the anterior horn cell, tone becomes correlated into a pattern

ABNORMALITIES OF TONUS AFTER COMPLETE TRANSECTION OF THE SPINAL CORD OF MAN

It is important to consider further the control of tonus by the isolated spinal cord of man after all influences from the brain are cut off The careful war-time observations of Riddoch (1917) make this possible He studied a number of previously healthy young adults in whom the spinal cord was completely transected in the upper thoracic region For the first few days following the injury no superficial or

deep reflexes could be elicited from the portion of the body innervated by the isolated cord The skin was dry The bladder became distended and the patients had to be catheterized

After a variable period of time, not more than seven days in some cases, reflex activity returned The reflexes in favorable cases became much more active than normal so that a slight cutaneous stimulation of the footpad produced a marked contraction of the flexors of both legs and of the musculature of the ventral body wall The bladder was evacuated at the same time and there was marked sweating over the whole area of skin innervated below the lesion Riddoch demonstrated that this was a mass reflex, the local reflex arcs lost their local sign and a sensory stimulus excited all the anterior horn cells to activity It suggested that cerebral control of the anterior horn cells, both somatic motor and autonomic, is predominantly an inhibitory one

On more careful examination it is quite evident that not all the somatic musculature innervated by the isolated segment took part in the mass reflex The muscles that contracted strongly were always the flexor muscles, indeed if any extensor reflexes were present in the legs, Riddoch was able to hypothesize that the cord was not completely severed

The response of the musculature in these cases followed a very definite pattern After a nocuous stimulus was applied to the plantar surface of one foot, both legs were sharply flexed and the abdominal musculature also contracted It has been suggested that this is the pattern of a primitive response to painful stimulation, withdrawing the legs from danger and protecting the vulnerable abdominal wall from injury

Babinski phenomenon Certainly this mass reflex is but an accentuation of the Babinski phenomenon which is elicited from the legs after injury of the cortico-spinal tracts The Babinski reflex is commonly thought of as a dorso-flexion of the great toe and fanning of the other toes on stimulation of the outer plantar surface of the foot When well developed, however, it is a general flexor response involving the ankle, knee and thigh Although the locus of the sensory area is on the outer plantar surface of the foot, a response may be obtained on painful stimulation over any portion of the leg or thigh as high as

the inguinal region The response obtained in spinal man differs from the Babinski only in a degree

Paraplegia in extension There is another clinical picture that must be considered with a discussion of the control of tonus by the isolated spinal cord If a tumor growing outside of the cord begins to press upon the spinal cord in the upper thoracic region, the pyramidal tracts, which appear to be particularly vulnerable to this type of injury, early become functionless This releases a tonic pattern controlled in the region of the brain stem from its normal inhibitory control and a hypertonus is present in the extensor musculature of the legs Loss of the cortico spinal control also produces a relative paralysis in the flexor muscles of the legs The legs are strongly abducted and extended The Babinski reflex may be elicited bilaterally and the abdominal reflexes are absent from the portion of the abdominal wall innervated below the injury Clonus may be demonstrated in the legs This syndrome is known as paraplegia in extension

Paraplegia in flexion If the tumor, however, continues to grow and press upon the cord until a physiological transection of the whole cord is produced, the pattern of tonus is quite changed until it is similar to that found in man after complete transection of the spinal cord The hypertonus of the extensor musculature is lost and no reflexes involving the extensor muscles can be obtained The tonus is now increased in the flexor muscles so that the legs are flexed at hip and knee Moreover, painful stimulation produces strong contraction of all the flexors innervated below the level of the lesion This is known as paraplegia in flexion

With these data it is possible to discuss the control of tonus by the isolated spinal cord In the case of paraplegia in extension the corticospinal tracts are functionless but other pathways connecting the brain and spinal cord are still normal The loss of the cortico spinal control releases tonic centers in the brain stem producing a picture of partial decerebration which will be discussed at some length under the heading of hemiplegia and injuries of the cortico spinal pathways

The abnormalities in tonus after complete transection of the cord and in cases of complete physiological transection due to pressure are identical Riddoch observed that in spinal man tonus always returned, first in the flexor muscles, then in the extensors and was always more marked in the flexors

The period of a-reflexia following the cord transection is due to the removal of efferent stimuli from the brain to the anterior horn cells The cells of the final common path are so dependent on this cerebral innervator that for a time the stimuli reaching the cells from spinal reflex arcs are not sufficient to produce reflex activity When the local mechanism does become self sufficient it overacts to a marked degree since inhibition is the predominant cerebral influence upon the anterior horn cells

The anterior horn cells innervating the extensor muscles are more under the influence of centres in the brain than are the cells innervating the flexor muscles In general it may be said that the flexor muscles produce the quick oscillatory movements, the extensor muscles contract the force of gravity The quick movements may be controlled by the spinal cord whereas that pattern of tone which has to do with the antigravity reflex is predominantly controlled by centres in the brain stem Since the tonus of the flexor muscles is less under the control of centres in the brain it recovers more quickly and completely in the isolated cord.

Further references to experimental work will make this thesis clearer The author has previously suggested (1928) that the act of walking may be thought of as composed of two factors A tonic contraction of the extensor muscular counteracts the force of gravity and supports the body from the ground, while alternating rhythmic flexor and extensor movements of the extremities produce a change of position and are responsible for locomotion Stepping is a fundamental activity of the nervous system,—rhythmic in nature and dependent on two peripheral, antagonistic forces, one tending toward flexion, the other toward extension Now one force, now the other becomes dominant, the antagonistic action being successively in a state of inhibition This tendency to rhythmic activity is, as shown by the experiments of Sherrington, a property of the isolated spinal cord The proprioceptive fibers from the muscles carry the afferent impulses responsible for reflex stepping Graham Brown (1912) demonstrated that even the integrity of the proprioceptive pathway was not necessary. The rhythmic tendency may be maintained on the motor side of the reflex arc and under certain conditions, such as asphyxia, these motor centres may be influenced to rhythmic activity

by substances contained in the blood stream after the manner of the respiratory center

The antigravity reflex on the other hand, is controlled by centres in the brain stem rather than the spinal cord In man the extensor muscles of the legs, trunk and neck preserve the body in the erect position It has already been observed that after transection of the cord in the thoracic region that tonus is most marked in the flexor muscles and the reflexes that may be elicited are flexor reflexes

There is more of the ability to stand perhaps in the case of laboratory mammals with the thoracic cord transected than in man After a cat has recovered from the shock and the posterior portion of the body is reflexly active it is able to support its weight on the legs for several seconds if the hind legs are abducted widely and placed as props There is no ability, however, for the tonus to accomodate itself to new positions and the hind-legs soon give way, even if the cat stands quietly

It may be mentioned that Foerster, in Germany, has observed some extensor responses in human patients after complete transection of the spinal cord, verified at operation Thus a crossed extensor reflex could be demonstrated in the legs The extensor responses do not appear until a period of years following the accident and he believes that the English investigators did not follow their cases long enough to observe them

In summary, quick, oscillatory flexor and extensor movements are a property of local reflex mechanisms in the spinal cord, the patterns of tonus regulating the postural reflex and involving the extensor musculature are controlled by centres in the brain stem The anterior horn cells controlling flexor tonus are less under the control of centres in the brain and recover more fully than the cells controlling extensor tonus when the spinal cord is made to function alone

MECHANISMS IN THE CORD CONTROLLING PATTERNS OF TONUS

Thus far only the activity of the lower portion of the cord after a transverse lesion in the thoracic region, has been discussed No cases of survival after transection of the cord in the upper cervical region in man occur This lesion isolates the muscles of respiration from the respiratory centre or injures the phrenic nuclei directly The activity

re
T
in
re
le
d
a

u
t
p
t
b
t
b
c
u

cl
w
co
ai
fl
of
m
pc
fl
be
st
by
co
in
dc
w
tl
a

is able to force the strongest steer on its side or back by passive movements of the animal's head

Hemiplegia produces in man an accentuation of tone in certain muscles of the extremities that may well serve as an adequate background for demonstration of the neck reflexes They occasionally may be brought out in these patients but are seen clearly in only a small number of subjects and the patterns are more complex and less predictable than in animals This is partly due to the fact that the spasticity in the arms is present in the flexor muscles rather than in the extensors as in four footed animals A discussion of the problem of patterns of tonic neck reflexes in man may be deferred till a later part of this paper where the whole question of hemiplegia is considered

The afferent impulses from the neck musculature must be conveyed by pathways to the somatic motor cells of the entire cord The effect of these stimuli is to increase the tonus in certain groups of muscles and decrease the tonus in others These impulses act upon a segmental reflex already described which is primarily responsible for muscle tone but by augmenting or decreasing the activity of this primary reflex are able to produce correlated tonic patterns It certainly is not possible to say that tone in general is increased or decreased by the activity of these influences

MECHANISMS IN THE BRAIN STEM CONTROLLING PATTERNS OF TONE

1 The vestibular apparatus

It is generally agreed at the present time by all investigators that the fundamental mechanisms for the production of tonic patterns lie in the mid brain and medulla The anatomy and physiology of these units are far from clearly understood Certain statements concerning the comparative development of the brain stem offer an explanation for the development of control of tonus in this region

The vestibular nerve and its connections in the brain stem appeared early phylogenetically, and assumed a dominating control over a former segmental organism In the case of the lowest vertebrates there is very little development of a brain and the segments of the cord are coordinated largely by intersegmental neurones The evolution of the vestibular nerve in higher forms introduced a new non-

segmental mechanism for the coordination of tonic activity With further differentiation of organisms a further cephalization of nervous function has continually taken place and the control of patterns of tonus has shifted from the region of the spinal cord and into the brain stem, particularly into the region dominated by the vestibular nerve

Since it is now generally believed that embryological development closely follows phylogenetic, the early differentiation of the vestibular mechanism in the human embryo assumes importance In the early human embryo, rapid growth of the nervous system first occurs in the region of the brain stem and this structure at one time has great relative size At first it is a simple tube, but eminences soon appear upon the surface due to rapid cell proliferation in localized areas The first areas undergoing this rapid growth are vestibular and the vestibular nuclei may be identified in all embryos over two somites In a similar manner the vestibulo-spinal tract and the medial longitudinal fasciculus are the first long pathways connecting the brain and the cord that receive their myelin sheaths

The importance of the vestibular centres in the production of tonic patterns was early demonstrated by experimental physiologists If the brain stem of the cat, for example, is completely transected at the level of the mid-brain an accentuation of tone appears in the extensor musculature of the body, the phenomenon is called decerebrate rigidity If the transverse section be made caudal to the vestibuli nuclei, severing their connections with the cord, tonus is completely lost in musculature It is clear, then, that transection of the brain stem at the level of the mid-brain frees the tonic mechanism from normal inhibitory control, that transection caudal to the vestibular nuclei abolishes the tonic patterns and produces a complete atonia of the musculature

The fundamental influences for the production of tonic patterns at the level of the vestibular nuclei are undoubtedly stimuli from the labyrinths although it is probable that other influences, for example, impulses from the cerebellum, reach this region and there is here the development of a correlation centre for tonus Magnus has studied the tonic labyrinthine reflexes The tonic neck reflexes were abolished by fixation of the neck of the experimental animal in a rigid plaster cast The preparation was then held in various positions in

space When the animal was placed in a supine position angle of the snout forty-five degrees above the horizontal p extensor tonus in the legs was maximal The position of mi tensor tonus was the prone position with the snout at an forty-five degrees below the horizontal plane With lateral of the body between pronation and supination and with var the angle of the snout with the horizontal, the extensor t intermediate, being greater or less according to the position mating the maximum or minimal extensor tonus There to believe that these reflexes depend on the otolithic appara utricle, since in the maximum position for these reflexes, th exert a maximal pull on the otolithic membrane, whereas in mal position they press upon the maculae

These tonic vestibular reflexes are difficult to demonstrat isolated from other factors producing tonic patterns They demonstrated in very young children and in patients with h Undoubtedly tonic reflexes from the labyrinths are importa ducing the tonic patterns in man The exact pattern, howe in different mammals

Two pathways from the vestibular nuclei carry impulses to cord as has already been explained The large cells of the Deiter's nucleus give rise to an uncrossed vestibulo spinal p axones from cells in the descending nucleus cross in the mi run caudal in the medial longitudinal fasciculus It has gested that the uncrossed pathway is excitatory, the crossed i

The previous discussion has suggested that the vestibu relay impulses to the spinal cord controlling tonus in relati tibular and other influences that reach these cells This ton regulates a unified pattern which can be varied by changing tion of the head The question then arises as to whether pulses may be said to increase or to decrease the tonus of the ture as a whole Although this possibility scarcely fits in idea of shifting patterns of tonus it certainly seems to be In the experimental animal, as previously described, transect neuraxis at the level of the mid-brain produces a great increas of the extensor musculature of the body The explanatic the apparatus controlling tonus is, in this way, freed fro

inhibitory control The same result is obtained on any section caudal to the mid-brain to the upper end of the vestibular nuclei If the vestibular nuclei are included in the section and severed in this way from their connections with the spinal cord, all tone in the musculature is lost There is evidence, therefore, that the influences from the vestibular nuclei in the normal animal reinforce tonus as controlled by the segmental stretch reflex This becomes important in considering the relief of pathological hypertonus

2 The mid-brain and the red nucleus

Structures in the mid-brain also have an influence upon patterns of tonus but their exact function has never been clearly understood Since the red nucleus is the most conspicuous group of cells in this region, to it have been ascribed various functions in connection with the postural reflex Opinions are very conflicting and only certain views may be introduced here that will help in the interpretation of the pathological syndromes that will be discussed later

Rademaker (1923) believed that removal of the fore-brain, cephalic to the red nucleus and leaving this structure intact, left the tonus of the musculature and the patterns of tonus entirely normal Removal of the red nucleus, on the other hand, produced a great increase in tonus in the extensor musculature and the picture of decerebrate rigidity He thought that, in the common laboratory mammal, tone was regulated in the final analysis, not by the fore-brain but by the red nucleus The cerebellum according to this observer had no influence upon tonus since no abnormalities followed its removal

The manner in which Rademaker considered that the red nucleus controlled tonus is important He felt that sensory impulses from the body musculature, labyrinths and neck muscles were synthesized in the brain-stem to produce patterns of tonus The labyrinthine and body influences were operative at the level of the red nucleus These reflexes involving tonus were called "righting" reflexes since they regulated the postures of the animal and tended in every case to bring the animal back into the optimum physiological posture with the body in a prone position and the eyes on a plane horizontal with the ground

The author has never agreed with these conclusions [illegible] rôle of the red nucleus or the phenom[illegible]

There has never been any evidence in Primates, including man, that unilateral or bilateral injury of the red nucleus produces a phenomenon resembling decerebrate rigidity Moreover transections of the brain-stem cephalic to the red nucleus produce abnormalities in tonus similar to those of the decerebrate animal This whole thesis will be elaborated in later portions of this review The righting reflexes represent merely the patterns of tonus that are discussed in this paper

The red nucleus receives influences from the corpus striatum and cerebellum In order to understand the part played by the red nucleus in the initiation and control of tonus the influence of the cerebellum and corpus striatum must be considered This will be done in sections which follow

3 Optic colliculi and optic influences upon tone

It seems clear that optic impulses finally influence the anterior horn cell and produce patterns of tonus regulated by visual stimuli These reflexes have been studied by several workers and it was thought that they were not important in lower mammals but assumed increasing control in Primates There is no agreement as to the pathways involved It would appear probable that this reflex is carried out at a low level in the reflex mechanism and involves the optic end stations in the mid-brain This seems the more probable inasmuch as there is a pathway from the optic colliculi to the cells of the final common path, the tecto-spinal tract Experiments, however, suggest that the reflex requires the integrity of the occipital lobe of the cerebral cortex Following removal of the visual cortex the animal turns the head to the affected side and walks in circles to that side Later, following the operation, a compensation sets in

With the rapid differentiation of the cerebral cortex in higher forms it is quite clear as will be demonstrated later, that the control of tonus has been taken over more and more by centres there The exact pathways required for the optic righting reflexes require further study Here their great importance in higher mammals may be emphasized

4 The rôle of the cerebellum in tonic reflexes

Here again the results of animal experimentation are conflicting Magnus and Rademaker assert that after complete removal of the cerebellum in man, tonus is quite normal in amount and distribution

Fortunately, in this case, we have direct observations following injuries of the cerebellum of man and those alone need be considered

Holmes (1917 and 1918) during the war was able to study and correlate the abnormalities following injury of the cerebellum in a large number of cases He concluded that practicaly all the abnormalities of muscle innervation could be explained on the basis of disturbances of tone Luciani (1915) had previously summarized the defects following lesions of the cerebellum under three headings, *asthenia* or a weakness and tendency to fatigue, *hypotonia* and *astasia* with staggering gait and intention tremor All these symptoms may be fundamentally reduced to one underlying cause, the hypotonia

A summary of Holmes' findings may be discussed at some length In the first place there was a definite hypotonia in the muscles which was at once apparent to the observer and was illustrated by photographs in his paper The hypotonia was marked in the first few days and then decreased, but as long as the patient showed any of the changes summarized in the following paragraphs, hypotonia could be said to be present When the lesion involved one half of the cerebellum the hypotonia was confined to that side of the body If the lesion was large enough to produce any symptoms at all the whole musculature of that side of the body was involved, not just one limb or one or more groups of muscles The hypotonia could be demonstrated in a number of different ways If the hypotonia limb was passively oscillated, its excursions were limited only by the ligaments and joints whereas the excursions of a normally tonic limb are checked to a certain extent by the muscle tone In severe cases the affected limb was unable to maintain any attitude without support There was a deficient elasticity of the muscles which could be demonstrated in the arm in the following manner When a normal arm is suddenly jerked from a position of extension into flexion it tends to spring back into its original position owing to the presence of tone in the extensors of the arm In the case of the abnormal arm, the forearm either remained in a position of flexion or swayed about uncertainly This could be demonstrated by another test The patient was instructed to resist by voluntary contraction the movement of the arm produced by sudden tap The affected arm showed greater excursion and oscillation than the normal one

The deep reflexes were also modified by the hypotonia A light tap, sufficient to evoke a knee jerk in a normal limb, often failed to evoke a response Also the knee jerk was pendular, undergoing a number of oscillations before it came to rest These after movements were due to a failure of after-shortening in the quadriceps extensor

The rebound phenomenon is probably due to a lack of tone in the antagonist muscles If the patient was told to pull the hand toward his mouth against resistance and the resistance suddenly removed, the normal hand was soon arrested by the action of the antagonists The affected hand did not stop in this manner and sprang back into the face

In the absence of normal tone, smooth coordinated movements were impossible because the element of fusion of small contractions was lacking This accounted for the disturbance of muscular contractions Fatigability was explained by the fact that in the absence of proper fusion of successive small contractions each contraction shortening the muscles must start at a lower level than that reached by its immediate predecessors and the power of the whole contraction must be less than that of a corresponding normal muscle Also undue fatigability occurred because the patient relied on voluntary contractions which fatigued without the assistance of tonus which is indefatigable There was often a delay of initiating contractions and relaxing them The hypotonic muscles had to take up slack which delayed contraction and relaxation

There are many demonstrable disorders of movement in cerebellar disease that may be traced to the disorganization of tone Thus there are errors in the direction, range and rate of movements and a loss of finer coordination of the movements of the fingers Tremor also occurs due to faulty fixation of the extremity These abnormalities of movement are well displayed in walking and the characteristic gait is due to a combination of the hypotonia and the efforts of the patient to make corrections for it The abnormal attitudes and postures probably compensate for loss of tone in the musculature of the abnormal side of the body Speech is grossly abnormal due to poor coordination of the musculature controlling phonation and articulation

These examples might be increased and the whole subject expanded further, but this review does not deal primarily with cerebellar disease Enough evidence has been presented to make it quite clear that ab-

normalities in tonus underlie most of the abnormal physical signs of cerebellar injuries in man Moreover, there is always a loss of tone No symptoms pointing to increase of tone have been observed in man The cerebellum is built up phylogenetically as a correlation and coordination structure in close connection with the vestibular nerve. One might expect, therefore, that it would control the finer coordination of tone and this seems to be the case Moreover the evidence presented here indicates that it normally augments the tonic reflexes of the lower reflex centers Tone as controlled by the cerebellum is a pattern coordinating the finer activity of all the muscles, participating in a movement

There is some evidence resting on experimental work that certain portions of the cerebellum give rise to impulses that tend to inhibit rather than augment the tonus of striated musculature For example, stimulation of the cephalic or caudal portion of the vermis produces an immediate and complete loss of extensor tonus in the decerebrate cat Moreover many observers attest that injuries or total removal of the cerebellum of animals does not produce a picture similar to that seen in man for symptoms of heightened tonus of the musculature are often observed The vermis is older phylogenetically and has quite different connections from the hemispheres of the cerebellum Efferent pathways from the vermis end around the cells of the vestibular nuclei, efferent fibers from the hemispheres end around the cells of the red nucleus Perhaps it is not too much to say that influences from the vermis inhibit tonus through connections with the vestibular nuclei while the hemispheres augment tonus through connections with the red nuclei The cerebellar hemispheres are so closely connected with the cerebral cortex that their interrelations in respect to influence upon tonus will be discussed in another section.

5. Control of tonus by the corpus striatum

Pathological processes injuring the corpus striatum and subthalamic nuclei closely allied with it, produce marked changes in tone in man, for example, in paralysis agitans and the post-encephalitic Parkinsonian syndrome The normal function of the corpus striatum in respect to the pattern of tonus is understood so poorly that it is useless to discuss it here Later the abnormal findings in man will be sum-

marized Animal experiments have yielded no information concerning the physiology of the corpus striatum inasmuch as injury or total removal gives rise to no abnormal behavior

6 *The influence of efferent pathways from the cerebral cortex upon tonic reflexes*

In man the activity of the central nervous system is dominated by the cerebral cortex In connection with the development of this structure one well known efferent path has arisen, the cortico-spinal or pyramidal pathway which carries impulses directly to the motor cells of the final common path This pathway has assumed great importance only in some Primates including man Even in lower monkeys removal of the cerebral motor cortex produces no permanent paralysis

With the development of Primates the cerebral cortex received a great impetus to further growth and differentiation Elliot-Smith (1927) believes that the immediate impetus was the development of adequate stereoscopic vision The positions of the eyes moved anteriorly and the snout decreased in size, permitting an overlap of the visual fields This gave for the first time a picture of the world in three dimensions At the same time the fore-legs were freed from their use as locomotor props and used to search for food and to carry it to the mouth and for climbing in the trees With the rapid growth of the cerebral cortex the motor efferent pathway became further differentiated Naturally it assumed particular control over the portions of the musculature that were being developed for skilled movements at that time It influenced little the trunk musculature and the proximal portion of the limbs A relatively large portion of the cerebral motor cortex is concerned with delicate movements of the hand The paralysis following total injury of the cortico-spinal tract is, therefore, a selective one, involving the arm much more than the leg and the hand more than the upper arm

Stimulation of the cortico spinal pathway elicits short, quick contractions that are predominantly flexor in type The execution of the delicate movements of the hands requires precise adjustments of tone in all the muscles around the joints By what mechanism is this tonic adjustment made?

Two other cortico-efferent pathways, the fronto-pontine and temporo-pontine tracts, arise in the cerebral cortex The fronto-pontine tract is made up of the axones of motor cells, somewhat smaller than the Betz cells, which lie anterior to the motor area particularly in the dorsal portion of the premotor area The position of the cells giving rise to the temporo-pontine tract is not yet known These tracts end around cells in the pontine nuclei and thus influences from the cerebral cortex reach the hemispheres of the cerebellum It seems probable that these pathways are concerned in the finer adjustments of tone required to carry out the delicate movements initiated by the cortico-spinal pathway In other words the cortico-spinal, fronto-pontine and temporo-pontine paths are initiated simultaneously for a precise coordination of finger movements

If this is true it may seem strange that the functional significance of the pontine pathways in man was not clear from earlier studies The reason for this is at once apparent In the internal capsule the pontine fibers lie close to, and on either side of, the cortico-spinal tract Any lesion here, and such a lesion is the most common cause of hemiplegia, would injure all these pathways together Thus in hemiplegia, as will be demonstrated, there is a selective paralysis and hypertonicity of the muscles of the body Clearly the only evidence of the different functions of these pathways could be obtained by injury to one without injury of the other One possible position for such a lesion would be localized in the cerebral cortex involving the cells of one of these pathways but not of the others

Adie and Critchley (1927) and many others have shown that a localized process in the dorsal portion of the frontal lobe, just anterior to the electrically responsive motor cortex, gave rise to characteristic abnormalities classified under three headings,—tonic perseveration, forced grasping and forced groping In a number of cases small tumors are responsible for the changes and the damaged area was accurately localized at operation or post mortem examination

The person with tonic perseveration finds that if he shakes hands or grasps an object with the affected hand he is quite unable to relax his grasp normally Forced grasping is another form of this same condition Sensory stimulation of reflex zones in the palm of the hand or on the flexor surface of the fingers will cause the fingers to close

upon the stimulating object very tightly, nor can this vigorous grasp be relaxed Forced groping is a more severe degree of this process If the normal side of the body is examined the abnormal hand involuntarily tries to interfere in this procedure Also when the patient finally succeeds in letting go of an object, the hand seeks for it and if possible picks it up again

Obviously these are abnormalities in the regulation of tonus, extremely complicated in type inasmuch as the lesion affects the higher association areas of the brain Animal experiments make these abnormal reactions more understandable King (1927), Langworthy (A, 1928) and others have shown that, after removal of the premotor area in the cat, abnormalities in tonus of the striated muscles of the contralateral extremities are present This suggests a control of the patterns of tone at the level of the cerebral cortex This control becomes greater in Primates as the cerebral cortex becomes extremely differentiated and dominates the functions of the organism As an objection to this theory concerning the role of the fronto pontine pathway in the control of tonus, it may be said that no abnormalities in tone follow the extensive resections of the frontal lobe of man performed by the surgeons at the present day The surgeon gives the motor cortex a wide berth and leaves the premotor area, of which we are speaking, intact

Summary of the Control of Tonus by the Central Nervous System

Tone is fundamentally a stretch reflex, dependent on the proper functioning of the segmental apparatus of the cord or brain stem Afferent impulses from the muscles influence the anterior horn cells and thus control tonus of the musculature

All portions of the nervous system control this primary reflex arc, coordinating tone into patterns for balance, movement and locomotion of the animal Afferent impulses from the deep neck musculature and from the vestibular and optic nerves are of particular importance, but as good a case could probably be made for other afferent stimuli For example, following a loud sound the eyes and head are turned in its direction and the tonus of the whole body oriented in reference to the stimulus The complicated ramifications of the sensory side of the reflex arcs cannot be followed, but it is possible to suggest the

nervous system at which the reflexes are synthesized and the efferent pathways to the cells of the final common path Thus the tonic neck reflexes are centred in the upper cervical segments of the cord and the vestibular at the level of the vestibular nuclei Many afferent impulses influencing tone reach the red nucleus and the vestibular nucleus and these seem to be particularly important in regulating tonus They not only produce patterns of tonus, the vestibular mechanism seems to augment the general tonus of muscles while the red nuclei have a control, predominantly inhibitory

A further, more subtle control of tonus is effected through the suprasegmental portions of the nervous system Injuries of the cerebellum in man produce hypotonia on the same side of the body as the lesion The corpus striatum in man controls tone in some way that is not understood Finally, the importance of the fronto-pontine and temporo-pontine pathways has been emphasized, acting through connections with the cerebellar hemispheres Other cerebral efferent connections are undoubtedly also used in tonic coordination Thus it has been suggested that optic righting reflexes are coordinated in the occipital lobes of the cerebral cortex

It has been emphasized sufficiently that tonic control above the segmental level is always of the nature of patterns involving suitable adjustments for balance in new positions Only at the level of the vestibular and red nuclei is there evidence of influences tending to augment or inhibit tonus as a whole Succeeding portions of this review will discuss abnormal patterns of tonus in man released by injuries of the nervous system

TREMOR IN RELATION TO ABNORMALITIES IN TONE

There is certain justification at this point in discussing tremors in man in relation to abnormalities in tone The static and kinetic tremors of patients with cerebellar injuries, the intention tremor of multiple sclerosis and the tremor associated with abnormalities of the corpora striata and other basal ganglia may be considered

Holmes (1917 and 1918) found that the tremors attributable to lesions of the cerebellum were always tremors of the unsupported parts of the body If a patient is told to bring the forefinger of the affected hand within an inch of his nose and maintain it in that posi-

tion a regular, almost rhythmical tremor of the whole arm quickly develops Normally the arm would be maintained in this position by the tonic contractions of all the muscle groups The tremor is due to absence of this tonus with the result that the new posture is maintained by voluntary contractions which fatigue easily Fatigue causes the new posture to be momentarily relaxed, following the relaxation the posture is regained by voluntary contractions This alternation of relaxation from fatigue and voluntary muscular efforts to maintain the posture is the causative factor of the static tremor

Kinetic tremor is a prominent symptom of cerebellar defect especially when the lesion involves the brachia conjunctiva Tremor may occur on any movement, the oscillations taking place in any of the planes of space It is primarily the result of faulty fixation by antagonistic musculature

The intention tremor of multiple sclerosis is similar to the kinetic tremor of cerebellar injury except that the oscillations in the latter condition are said to be less sharply defined It is probable that they are due to identical defects since the tremor of multiple sclerosis is usually due to the involvement of cerebellar pathways, particularly of the superior peduncles and the mid-brain by the pathological process The only result of injury to the red nucleus in man that has been observed is an intention tremor of the extremities of the opposite side of the body

Walshe (1929) recently analyzed the tremor present following injuries to the corpus striatum and basal ganglia, for example, in paralysis agitans and the post-encephalitic Parkinsonian syndrome The two leading abnormalities in these patients are hypertonus and tremor The separation between the tremor and rigidity is not an absolute one for the cog-wheel phenomenon is undoubtedly to be attributed to a tremor which may not be clearly evident

English clinicians have insisted for a considerable time that the tremor in these conditions is dependent upon the integrity of the cerebral motor cortex and cortico spinal pathway If a hemiplegia supervene in these cases the tremor disappears and never returns in the opposite extremities Walshe then questioned whether the tremor was a new phenomenon produced by the lesion or whether it was evidence of normal activity of the nervous system unmasked by the injury Many data favored the latter view

The quick movements normally initiated by the cerebral motor cortex are not smooth contractions but are always carried out as a curve exhibiting waves This may be observed by watching the slow flexion of one of the fingers and the irregularity may be recorded graphically The rate of these waves is from eight to ten per second and they are observable only in slow movements Moreover faradic stimulation of the cerebral cortex of animals at a rate of sixty per second produces similar waves of contraction in the musculature occurring at the rate of about ten per second Denny-Brown (1929) found that the usual rhythm of clonus on cortical stimulation at rapid rates is from two to five per second

Is there any relationship then between this normal cortical rhythm and the tremor present in paralysis agitans? If the tremor is followed in these cases and recorded graphically from its first appearance it is found to develop upon the basis of the normal waves of voluntary contraction and to be a simple accentuation of them

Walshe suggests that the waves seen in the curves of slow voluntary contraction express a slow rate of cortical discharge while the disappearance of these waves in rapid movement is due to the more rapid rate of discharge from the cortex In Parkinsonian rigidity without visible tremor this wave fusion occurs less readily and gives rise to the cog-wheel phenomenon while with manifest tremor the fusion does not occur at all or only when extensive and rapid muscular contractions occur

In summary, the static and kinetic tremors of cerebellar disease and the intention tremor of multiple sclerosis are fundamentally attributable to abnormalities in tone In like manner the tremor of paralysis agitans represents influences from the cerebral cortex unsupported by the normal tonic background

ABNORMALITIES IN TONUS DEMONSTRABLE IN A PATIENT WITH HEMIPLEGIA

The next sections of this paper deal with common abnormalities of tone following injury of the central nervous system of man The syndromes following partial and complete transection of the spinal cord have already been considered The author obtained much of the material for the physiological analysis of hemiplegia and the Parkin-

somian defects from a recent brilliant paper by Walshe (1929), he wishes to express his grateful acknowledgment

Hemiplegia, one of the most common diseases seen in a neurological clinic, is also one of the most profitable conditions to interpret in terms of modern experimental physiology All the abnormalities in the motor system and reflexes found in hemiplegia may be grouped under three headings, paralysis, abnormalities in tone, and release from cerebral control of reflexes presided over by the brain-stem and cord The last group of abnormal reflexes need not concern us here except in so far as it is related to abnormalities in tone

The paralysis following lesion of the pyramidal path has already been discussed from the standpoint of the development of the cerebral motor cortex Since the impulses from this region do not exert an equal influence over the musculature the paralysis is a selective one The facial muscles are the most severely paralyzed of any of the musculature innervated by the cranial nerves Since the cells supplying the upper portion of the face receive bilateral pyramidal impulses, the upper portion of the face is spared The extraocular muscles, muscles of mastication, muscles of the pharynx and larynx may show a weakness but no enduring paralysis after injury of one pyramidal tract The injury is more severe in the case of hypoglossal innervation and the tongue usually deviates markedly toward the paralyzed side

The paralysis is more marked in the upper extremity than in the lower and in both extremities is more severe in the distal than in the proximal muscle groups In the arm, in order of severity, the paralysis affects all skilled and isolated movements of the hand and fingers, extension of the wrist and fingers, supination of the forearm, abduction and elevation of the upper arm In the leg the weakest movements are dorsiflexion of the foot and toes and flexion at the proximal joints

The amount of hypertonus does not necessarily correspond to the degree of spasticity Cases of severe hypertonus are seen with a great deal of power of movement remaining, and the opposite often occurs Under the heading of hypertonus, hyperactive tendon reflexes, clonus, and associative movements or abnormal patterns of tonus, may be considered

The hypertonus, like the loss of voluntary movement, is not present

equally in all the musculature of the body but is selective In general, it may be said that the increased tonus is present in the flexor muscles of the arms and the extensor muscles of the leg In the arm it is maximal in the flexors of wrist and fingers, the flexors and pronators of the forearm and the abductors of the upper arm In the leg it is greatest in the plantar flexors of foot and toes, in the knee extensors and in the thigh abductors

The quality of the spasticity may be learned by an attempt passively to flex the knee The initial five or ten degrees of flexion can often be carried out quite without resistance The muscle then develops tension and opposes the movement through another thirty degrees when this resistance melts away and the remainder of the movement is carried out quite easily This is known as the "clasp knife" phenomenon

The deep tendon reflexes are markedly accentuated in cases of hemiplegia The knee jerk may be taken as an example The quadriceps contracts strongly and there occurs a slow relaxation so that the graphic record shows a marked hump which is characteristic

Clonus may sometimes be elicited from the hypertonic muscles It is most commonly obtained from the gastrocnemius-soleus muscles as an ankle clonus and occasionally from the quadriceps as patellar clonus It is rarely obtained from the musculature of the arm and when it is, may be produced by sudden stretch of the flexor muscles, particularly the wrist flexors Clonus consists of alternate impulses of contraction and inhibition in the muscle It may be stopped at once by relieving the stretch upon the muscle

The associated reactions seen in hemiplegia are accentuations of patterns of tone controlled by centres in the brain-stem and cord They are remarkably difficult to elicit in most cases but when present are of much physiological interest They are usually demonstrated in the arm During a yawn the hemiplegic arm slowly rises in front of the chest, the wrist extends and the fingers fan This posture is maintained as long as the yawning lasts Voluntary movements on the normal side are often associated with changes on the hemiplegic side If the patient looks straight ahead and clenches the normal fist, the spastic arm which has been held adducted and slightly flexed at the elbow, wrist and fingers becomes further flexed If the patient's

head is first rotated toward the hemiplegic side, the spastic arm becomes extended and abducted If the patient's head is rotated toward the sound side and he then makes a fist the spastic arm becomes increasingly adducted and flexed

Acute rotation of the head against resistance toward the hemiplegic side sometimes produces extension and abduction of the affected arm, while rotation to the healthy side is followed by increased flexion and adduction Similar changes in the position of the body may be produced by stimulation of the vestibular mechanism Thus the hypertonus of hemiplegia is influenced by stimuli arising in the labyrinths, deep neck muscles and the arm muscles of the normal side

These abnormalities of tonus present in the hemiplegic patient may then be analyzed in the light of our knowledge of the physiology of tone and its control by the nervous system The hypertonus of the musculature is abolished by posterior root section or by intramuscular injection of novacaine in such strengths as paralyse conduction in the sensory nerves of the muscle and leave the motor pathway normal It is dependent, therefore, on sensory impulses from the muscles themselves, and is a stretch reflex similar to that which has been discussed in connection with the segmental tonus mechanism of the cord Moreover the hypertonus has many remarkable resemblances to that seen in the decerebrate animal

The normal stimulus for the hypertonus is stretch of the muscle just as it is the stimulus for tonus in a normal muscle The relative nonfatigability of the response depends on the asynchronous nature of the stimulus and upon the fact that the affected muscle fibers are the relatively slow contracting, fatigue resisting, red muscle fibers If a muscle already engaged in a slight tonic contraction in response to a stretch be passively lengthened, its initial response is the development of increased tension, but as the lengthening is continued this response is inhibited, the tonic contraction ceases and the observer who has been manipulating the limb feels the resistance of the muscle melt and disappear This explains the clasp knife rigidity of hypertonic muscle

If the two ends of the muscle are passively approximated and the muscle takes up a new and shorter length, it is again found to resume tonic contraction and to preserve the new posture passively imposed upon it This is also a manifestation of the stretch reflex For when

the limb is released its weight tends slightly to stretch the shortened muscle and the stretch receptors are once more stimulated.

Walshe feels that the hypertonus found in hemiplegia is very similar to that present in the decerebrate animal The distribution of tonus, however, is markedly different In the animal the hypertonus is found in the extensor musculature or in the antigravity muscles In the hemiplegic the increased tone involves the extensor musculature of the legs but the flexor muscles of the arms The problem, therefore, is to explain the hypertonus of the flexor muscles of the arm in hemiplegia Walshe points out that the arm in man is no longer used as a locomotor prop but hangs freely at the side In this position it is the flexor muscles that are most stimulated by gravity and he believes that the tonic mechanism in the arm of man has been reset in the flexor rather than in the extensor muscles

In confirmation he cites the study by Richter and Bartemeier (1926) of the decerebrate sloth This animal hangs constantly by all four legs from the limbs of trees In this position the flexor muscles are the antigravity muscles After decerebration the hypertonus is present in the flexor musculature

Since the removal of the cerebral motor cortex, even in the higher apes, produces no picture similar to hemiplegia or decerebrate rigidity in animals, it must be assumed that the cortico-efferent pathways in man have assumed a greater control not only over the contraction of muscles but also over the tone of muscles than in animals This indeed seems to be the case Even in laboratory mammals, however, injury of the fronto-pontine tract produces abnormalities in tonus in the contralateral leg musculature

The question then arises as to whether hemiplegia is exactly equivalent to a half decerebration Obviously the lesion does not remove the entire fore-brain as in experimental animals and it seems logical to speak of hemiplegia as a partial decerebration, or to say that hemiplegia produces physiological changes in tone similar to those seen in the decerebrate animal Decerebrate rigidity was originally defined by Sherrington in terms of a level of the nervous system "Decerebrate rigidity is a condition which ensues on removal of the forebrain by transection of any of the various levels in the mesencephalon or in the thalamencephalon in its hinder part" (Sherrington, 1906)

Have any cases been reported of true decerebrate rigidity in man? In 1920 Wilson described tonic fits associated with marked extensor hypertonus of both the arms and legs He suggested that a physiological decerebration was operative in these cases

Walshe (1923) described a case of what he believed was a complete decerebration in man resulting from a supracellar cyst which pressed against the mid-brain producing the equivalent of an experimental transection The abnormalities in this case were precisely those of a double hemiplegia But the early pressure in such a case would first injure the cortico efferent pathways in the cerebral peduncles and it is probable that this case was simply a quadriplegia and not a decerebrated man It is probable that no true cases of human decerebration have been reported

THEORETICAL AND PRACTICAL SUGGESTIONS FOR THE TREATMENT OF HEMIPLEGIA

The theoretical data that may be discussed in connection with the treatment of hemiplegia have already been developed in earlier portions of this paper and may be considered first

The type of patient that would be selected for rehabilitation obviously would be a young individual who might be restored to a useful position in the community The aged arteriosclerotics are thus excluded from consideration

The most favorable prospects would be those cases in which a great deal of voluntary power remains in the muscles but in whom the hypertonus is so great that this power is inadequately utilized Many cases of paraplegia due to luetic meningo-myelitis of the cord have a great deal of residual power in the legs which is overshadowed by the hypertonus Even in capsular lesions the ratio between paralysis and spasticity is a variable one Finally there are the cases of circumscribed cortical injury with abnormalities in tone but little or no paralysis

Foerster (1913) believes that infantile paraplegias offer the best opportunity for improvement by therapeutic and operative procedures In these cases there is often considerable latent voluntary power in the leg musculature, the extent of which cannot be gauged before the increased tonus is relieved Unfortunately many of these

patients show considerable corpus striatal and basal ganglia involvement These are unfavorable for operative intervention for reasons which will become apparent in later portions of this review

To return to theoretical treatment of uncomplicated hemiplegias or paraplegias, hypertonus is due primarily to the activity of the segmental mechanism, inasmuch as cutting the posterior roots abolishes the tonus If Denny-Brown's theory is correct that neuro-tendonous endings in the muscle give rise to impulses that augment tone and the neuromuscular spindles to impulses that would inhibit tone, it would be logical to decrease selectively the activity of the neurotendonous endings Unfortunately such a selective injury is at present impossible inasmuch as the tendon extends into the very substance of the muscle

A review of the portions of the nervous system having a part in reflex tonus has suggested that tonus controlled by the cord as a whole or by the brain, consists in every case of patterns However there is some evidence to suggest that certain portions of the nervous system tend to give rise to stimuli which augment tone as a whole This is true of the vestibular nuclei Moreover lesions of the cerebellum of man give rise to hypotonia It seems quite possible that cutting one small tract in the brain stem might relieve the increased tonus entirely, leaving no abnormal tonic pattern This is certainly worthy of the experimental test Unfortunately the control of tonus varies so markedly in different animals that it would be difficult to apply the experimental results to man

The more practical aspects of this problem may now be dealt with Foerster has for years been interested in this problem and his results will form the basis of discussion The reader is referred to a paper published in 1913 and to an address before the American college of Surgeons in 1930

Since tonus is dependent upon the activity of the segmental reflex arc, Foerster proposed and carried out posterior root section in a number of cases Obviously the question of the number of posterior roots that should be cut is a difficult one One would wish to decrease the degree of tonus in the musculature to normal Foerster found that in cases which showed an obvious hypotonia following the operation tone gradually increased and finally became greater than normal

again Moreover in cases where there was some voluntary movement, hypotonia of the extremity would not be desirable

It is interesting to speculate concerning the effect upon voluntary activity of the legs if the pyramidal tract were still intact but all the posterior roots cut Foerster maintains that in such a case the patient might learn to walk but as soon as voluntary attention upon the legs was relaxed for a second, tone would be lost in the legs and the subject would fall A severe case of tabes with almost complete involvement of the lumbar and sacral roots would almost answer the description except that in this case the lesion is a gradually developing one

Section of posterior roots for the relief of spasticity is, therefore, open to a number of objections The tone may be decreased by the operation below the normal and may gradually increase until marked hypertonus is again present

Posterior root section is particularly indicated in cases of paraplegia in flexion with no voluntary control of the musculature Under these conditions the increased tonus may be so great that the muscles are extremely painful, and the pain is accentuated by cramp like contraction of the musculature Section of a number of posterior roots innervating the legs produces a hypotonia relieving the pain entirely It also abolishes the annoying involuntary movements of the legs and makes it possible for them to be placed in an extended position which is much more satisfactory

When certain voluntary power is present in an extremity posterior root section is certainly not the operation of choice Here one should aim at correcting the deformity and decreasing the tone in the particular muscles involved The results of this effort are usually more satisfactory in the case of the leg than the arm Foerster is able to demonstrate in photographs and moving-picture films cases showing marked improvements

The foot in hemiplegia is usually ventro flexed and internally rotated Lengthening the Achilles tendon and further tendon operations, if necessary, correct this deformity The leg is greatly adducted and this adduction is so marked in cases of paraplegia that it, in itself, is a serious obstacle to locomotion Section of the nerves to the adductor musculature of the thigh overcomes this contracture

The problem of the hypertonicity in the quadriceps is a more difficult one Foerster exposes the nerve to the muscle and cuts a few fibers at a time until the knee jerk is reduced to an approximation of normal The knee jerk serves as a delicate test of the number of nerve fibers to be cut Naturally the operation must be performed with local anesthesia

By means of transplanting tendons and partially or totally deafferenting muscles good results may be obtained in the lower extremities when considerable voluntary power remains Similar methods may be applied to the arm but there the technical difficulties are greater Here, extension of the fingers may be obtained but the power of supination is difficult to restore

It may be said that the position of the hypertonic extremities in a hemiplegic with great decrease of voluntary movement is perhaps ideal The extended leg makes some degree of locomotion possible and the arm is held flexed out of harm's way An extended and paralyzed arm would be much more of a liability than a flexed one

Foerster believes that the hypertonicity develops in the muscles that are most relaxed, the flexors of the arms and the extensors of the leg If Denny-Brown's hypothesis is again considered increased tone would develop in those muscles which are not stretched sufficiently to call the inhibitory impulses from the neuromuscular spindles into activity Foerster found that the pattern of tone may be influenced in these cases by changing the position of the limb, particularly in patients in whom the excess tonicity was just developing If the legs were kept flexed for a considerable period the spasticity was present in the flexor muscular With our present physiological understanding of patterns of tonus we cannot attach too much value to this method of treatment It is important, however, that from the first days of paralysis the fingers and wrists be held in extension by apparatus in order that they be as useful as possible The same applies to the foot In children, especially, a marked shortening of the achilles tendon should be avoided

The operations suggested here require a great deal of time and skill They are undoubtedly important in cases that are young and have a possibility of some voluntary function

ABNORMALITIES IN TONUS DEMONSTRABLE IN PATIENTS WITH PARKINSON'S DISEASE

In the description of cases of paralysis agitans and the post-encephalitic Parkinsonian syndrome and in the physiological interpretation of the abnormalities, Walshe will again be quoted Three marked symptoms are found in these patients,—tremor, rigidity and a decrease in the range and force of all movements The tremor has already been considered

The decrease in movement in these cases involves all groups of striated muscles although to various degrees Walshe points out that there is a decrease in the force, rate and range of all voluntary movements There is almost an extinction of movements of facial expression and of the limb gestures that accompany them and also a loss of all associated movements such as swinging the arms in walking

It is further believed that it is the force required to carry out a movement that determines the degree to which the movement is decreased Thus small amounts of force are required to produce the normal fleeting expressions of the face and these are diminished early, producing the mask-like face Similarly associated movements require little force The fact that facial expression and associated movements are not completely lost is clear from the fact that they appear again if the stimulus is great enough Thus a smile may slowly spread over the face of the patient, remain an abnormally long time and then slowly fade again Under stress of circumstances the patient may lengthen his stride and swing his arms in a free and rapid action

Movements are slow in initiation and performance and are often brought to a stop before completion In the performance of an alternating movement such as flexion and extension of the elbow there is a progressive decrease in speed and range of the movement until it degenerates to the oscillation of the tremor In the case of a subject with paralysis agitans, an increasing effort is required to ensure completion of a movement

The hypertonus found in these cases differs in several ways from that present in the hemiplegic In Parkinson's disease the rigidity is not a selective one but involves all the musculature of the extremities and trunk, although it is more marked in the flexor muscles It also

is present in all the muscles innervated by the cranial nerves It remains throughout the full range of movement and there is no decrease when the stretch on the muscle becomes great The clasp-knife phenomenon, therefore, is not present One does feel the tonus vary in a series of waves when the muscles are passively stretched This is the cog-wheel phenomenon which is due to the presence of the underlying tremor No stimuli from the neck muscles or vestibular mechanism cause the tone to change in any manner

The two types of increased tonus do have features in common In Parkinson's disease, just as in hemiplegia, the hypertonus is completely abolished in an extremity by cutting the posterior roots Moreover injection of one per cent novocaine into the muscle in sufficient quantity to paralyze the afferent sensory mechanism and to leave the motor side of the reflex arc intact, abolishes the tonus The rigidity in Parkinson's disease is, therefore, dependent upon a segmental reflex arc and the afferent stimuli from the muscles involved Abnormal stretch of the muscle, on the other hand, does not elicit an inhibitory reflex The deep tendon reflexes are active but seldom show the hyperactivity of hemiplegia

The rigidity and decrease of voluntary movement have a close relationship to each other, indeed the damping down of voluntary movement is due to the difficulty of overcoming the rigidity of muscle This was shown by Walshe very clearly If the normal individual is asked to flex and extend the elbow an indefinite number of times the movement is continued for a considerable time before fatigue sets in and the range, rate and strength of movement remains relatively constant In the case with rigidity the task is begun with a great deal of effort and the amplitude decreases almost at once so that after three or four beats the range has decreased to the extent of the oscillations of the tremor Suppose now that novocaine is injected into the flexors and extensors of the elbow to paralyze the sensory endings and abolish the increased tone The movement of flexion and extension of the elbow is now as free as in the normal individual Hypertonus is here the factor that restricts voluntary movement and abolition of the rigidity makes free movement again possible This explains why motor power is decreased in ratio to the normal force required to initiate it When the stimulus is great enough movements break through

The disturbances in gait are understandable in this same way The rigid subject cannot adjust his centre of gravity with normal activity and his rapid short steps are an effort to preserve his balance

THEORETICAL AND PRACTICAL CONSIDERATIONS IN THE TREATMENT OF THE PARKINSONIAN PATIENT

It has been found that certain drugs such as stramonium and hyoscin, when given to the patient in relatively large quantities, tend to decrease the rigidity of the musculature and, with the decrease in tone, voluntary movements become more free Drugs have little effect upon the tremor Cobb (1922) found that it was sometimes completely stopped by scopolamin

There is, at the present time, no means of treatment for the tremor It is known that section of the cortico efferent pathways abolishes the tremor completely but this is scarcely useful in the way of therapy

The fundamental abnormality in this condition is uniform hypertonus of the musculature and were this relieved, movements could be carried out quite easily and the patient would be normal except for the tremor Perhaps investigations aiming to relieve the increased tonus might attempt surgical methods, cutting pathways which appear normally to augment generally the tonus of the entire musculature Unfortunately animal experimentation is not an entirely satisfactory approach to this problem for reasons already discussed However studies along this line should be carried farther

SUMMARY

Injuries to the central nervous system of man often produce marked abnormalities of tone in the striated musculature of the body The specific changes after lesions in certain definite portions such as the spinal cord or cerebellum have been discussed Two common abnormalities, showing as prominent symptoms increased tonus, hemiplegia and Parkinson's disease were analyzed from the viewpoints of recent studies of the physiology of tone and possible treatment is suggested

BIBLIOGRAPHY

ADIE, W J , AND M CRITCHLEY 1927 Forced grasping and groping Brain, vol 50, p 142

is present in all the muscles innervated by the cranial nerves It remains throughout the full range of movement and there is no decrease when the stretch on the muscle becomes great The clasp-knife phenomenon, therefore, is not present One does feel the tonus vary in a series of waves when the muscles are passively stretched This is the cog-wheel phenomenon which is due to the presence of the underlying tremor. No stimuli from the neck muscles or vestibular mechanism cause the tone to change in any manner

The two types of increased tonus do have features in common In Parkinson's disease, just as in hemiplegia, the hypertonus is completely abolished in an extremity by cutting the posterior roots Moreover injection of one per cent novocaine into the muscle in sufficient quantity to paralyze the afferent sensory mechanism and to leave the motor side of the reflex arc intact, abolishes the tonus The rigidity in Parkinson's disease is, therefore, dependent upon a segmental reflex arc and the afferent stimuli from the muscles involved Abnormal stretch of the muscle, on the other hand, does not elicit an inhibitory reflex The deep tendon reflexes are active but seldom show the hyperactivity of hemiplegia

The rigidity and decrease of voluntary movement have a close relationship to each other, indeed the damping down of voluntary movement is due to the difficulty of overcoming the rigidity of muscle This was shown by Walshe very clearly If the normal individual is asked to flex and extend the elbow an indefinite number of times the movement is continued for a considerable time before fatigue sets in and the range, rate and strength of movement remains relatively constant In the case with rigidity the task is begun with a great deal of effort and the amplitude decreases almost at once so that after three or four beats the range has decreased to the extent of the oscillations of the tremor Suppose now that novocaine is injected into the flexors and extensors of the elbow to paralyze the sensory endings and abolish the increased tone The movement of flexion and extension of the elbow is now as free as in the normal individual Hypertonus is here the factor that restricts voluntary movement and abolition of the rigidity makes free movement again possible This explains why motor power is decreased in ratio to the normal force required to initiate it When the stimulus is great enough movements break through

The disturbances in gait are understandable in this same way The rigid subject cannot adjust his centre of gravity with normal activity and his rapid short steps are an effort to preserve his balance

THEORETICAL AND PRACTICAL CONSIDERATIONS IN THE TREATMENT OF THE PARKINSONIAN PATIENT

It has been found that certain drugs such as stramonium and hyoscin, when given to the patient in relatively large quantities, tend to decrease the rigidity of the musculature and, with the decrease in tone, voluntary movements become more free Drugs have little effect upon the tremor Cobb (1922) found that it was sometimes completely stopped by scopolamin

There is, at the present time, no means of treatment for the tremor It is known that section of the cortico efferent pathways abolishes the tremor completely but this is scarcely useful in the way of therapy

The fundamental abnormality in this condition is uniform hypertonus of the musculature and were this relieved, movements could be carried out quite easily and the patient would be normal except for the tremor Perhaps investigations aiming to relieve the increased tonus might attempt surgical methods, cutting pathways which appear normally to augment generally the tonus of the entire musculature Unfortunately animal experimentation is not an entirely satisfactory approach to this problem for reasons already discussed However studies along this line should be carried farther

SUMMARY

Injuries to the central nervous system of man often produce marked abnormalities of tone in the striated musculature of the body The specific changes after lesions in certain definite portions such as the spinal cord or cerebellum have been discussed Two common abnormalities, showing as prominent symptoms increased tonus, hemiplegia and Parkinson's disease were analyzed from the viewpoints of recent studies of the physiology of tone and possible treatment is suggested

BIBLIOGRAPHY

ADIE, W J, AND M CRITCHLEY 1927 Forced grasping and groping Brain, vol 50 p 142

BROWN, T GRAHAM 1912 The factors in rhythmic activity of the nervous system Proc Roy Soc , B, vol 85, p 278

COBB, STANLEY 1922 Electro myographic studies of paralysis agitans Arch Neurol and Psychiat , vol 8, p 247

Idem 1925 Review on the tonus of skeletal muscle Physiol Rev , vol 5, p 518

DENNY-BROWN, D 1929 On the nature of postural reflexes Brain, vol 104, p 252

FOERSTER, O 1913 Relations between spasticity and paralysis in spastic paralysis 17th Intern Cong of Med London, Sect 11, Neuropathology, part 2, p 55

HERRICK, C J , AND G E COGHILL 1915 The development of reflex mechanisms in amblystoma Jour Comp Neurol , vol 25, p 65

HINES, M , AND S S TOWER 1928 Studies on the innervation of skeletal muscles 2 Of muscle spindles in certain muscles of the kitten Bull Johns Hopkins Hosp , vol 42, p 264

HOLMES, G 1917 The symptoms of acute cerebellar injuries due to gunshot injuries Brain, vol 40, p 461

Idem 1918 The symptoms of acute cerebellar injuries due to gunshot injuries

KING, W T 1927 Observations on the role of the cerebral cortex in the control of the postural reflex Amer Journ Physiol , vol 80, p 311

LANGWORTHY, O R 1928 The control of posture by the central nervous system Physiol Rev , vol 8, p 151

Idem A 1928 The area frontalis of the cerebral cortex of the cat, its minute structure and physiological evidence of its control of the postural reflex Bull Johns Hopkins Hosp , vol 42, p 20

Idem 1929 A correlated study of the development of reflex activity in fetal and young kittens and the myelinization of tracts in the nervous system Contrib to Embryol No 114, Carnegie Inst Wash , vol 20, p 127

Idem, AND C P RICHTER 1930 The influence of efferent cerebral pathways upon the sympathetic nervous system Brain, vol 53, p 178

LUCIANI, L 1915 Human physiology, vol 3, London

MAGNUS, R 1924 Korperstellung Julius Springer, Berlin

RADEMAKER, G G J 1923 Der Rote Kern, die normale Tonusverteilung and die Stellfunktion Klin Wochenschr , vol 2, p 404

RICHTER, C P , AND L H BARTEMEIER 1926 Decerebrate rigidity in the sloth Brain, vol 49, p 207

RIDDOCH, G 1917 The reflex functions of the completely divided spinal cord in man, compared with those associated with less severe lesions Brain, vol 40, p 264

SHERRINGTON, C J 1906 The integrative action of the central nervous system Yale University Press

SMITH, G ELLIOT 1927 The evolution of man Oxford Univ Press

WALSHE, F M R 1923 *Decerebrate rigidity in man* Arch Neurol and Psychiat vol 10, p 1

Idem 1929 Physiological analysis of some clinically observed disorders of movement Oliver-Sharpey lectures Lancet, vol 1, p 963

WILSON, S A K 1914 An experimental research into the anatomy and physiology of the corpus striatum Brain, vol 36, p 427

Idem, AND F M R WALSHE 1914 The phenomenon of tonic innervation and its relation to motor aproxia Brain, vol 37, p 199

Idem 1920 On decerebrate rigidity in man and the occurrence of tonic fits Brain, vol 43, p 220

A Monumental Work Now Comple

PETERS and VAN SLYKE'S

Quantitative Clinical Chemistry (*In Two Volum*

Volume I Interpretations

A Reference Book for the Study and Guide-book for the Use of the Clinical Laboratory (Published March 1931)

Volume II Methods

A Handbook for the Laboratory and Guide-book for Technical Procedures (Published February 1932)

"INTERPRETATIONS" is a volume of some 1300 pages, well illustrated, describing the physiological rôle of each substance of importance in clinical chemistry together with its significance in diagnosis and therapy "No physician can practice medicine without a thorough acquaintance with the information presented in this monumental text-book" says William S Collens in N Y State Journal of Medicine The work is illustrated and includes extensive bibliographies **Volume I $12 00**

"METHODS" is a work of 1000 with nearly a hundred illustratior describes fully and in detail, step b all the analytical laboratory proc pertinent to clinical medicine It clinical laboratory worker's "I Within" It deals with technique cedures, the use of apparatus and ment Like its companion-volume the impress of the best scholarship day As indispensable to efficient ratory work as proper equipm glass-ware **Volume II $**

Both Volumes, Ordered and Shipped Together, $20 0

*** Note To enable those who purchased Volume I prior to publication of Volume II, to purchase Volume II at the "combination rate," Volume II will be sold until June 30, 1932, for $8 00**

Watch for This Page in Each Issue, to Keep Informed on New Contributions to Fundamental Science

NEW AND FORTHCOMING BOOKS

This List Compiled April 10, 1932

PUBLISHED SINCE FEBRUARY 1, 1932

MAN AND MICROBES by DR STANHOPE BAYNE-JONES (Number Three in the CENTURY OF PROGRESS series). $1 00

Cloth, 5 x 7½, viii + 128 pages.

AMERICAN UNIVERSITIES AND COLLEGES by DR. JOHN H. MACCRACKEN $4 00

Cloth, 6 x 9, vii + 1066 pages Index.

THE LAST CRUISE OF THE CARNEGIE by J. HARLAND PAUL $5 00

Cloth, 6 x 9, viii + 331 pages. Extensively illustrated.

MEET THE SCIENCES by WILLIAM MARIAS MALISOFF $2 50

Cloth, 5½ x 8¾, 196 pages Bibliography Glossary.

SUN YAT-SEN VERSUS COMMUNISM by DR. MAURICE WILLIAM $5.00

Cloth, 6 x 9¼, viii + 232 pages. Index.

PRIMARY CARCINOMA OF THE LUNG by DR. B. M FRIED $5 00

Cloth, 6 x 9¼, ix + 247 pages. Bibliography. Index

ELECTRICAL PHENOMENA IN GASES by KARL KELCHNER DARROW, PH D. $8 00

Cloth, 6 x 9, xiii + 492 pages. Index

MICROSCOPIC SLIDE PRECIPITATION TESTS by DR B S. KLINE $2 50

Cloth, 6 x 9¼, vii + 99 pages Index

FORTHCOMING

QUANTITATIVE CLINICAL CHEMISTRY—Methods—by DR JOHN P. PETERS AND DR. DONALD D VAN SLYKE, to be published in May, 1932, probable price, $10 00

EVOLUTION YESTERDAY AND TODAY (Number four in the CENTURY OF PROGRESS series), by HORATIO H NEWMAN, Ph D , to be published later part of April 1932, price $1 00

AGENCIES IN FOREIGN COUNTRIES

B WESTERMANN CO , INC , Jerusalemerstr 56, Berlin SW 68, Germany

MARUZEN COMPANY, 6 Nihonbashi Tori-Nichome, Tokyo, Japan

BAILLIÈRE, TINDALL & COX, 8 Henrietta Street, Covent Garden, London, W C 2, England

ANGUS & ROBERTSON, LTD , 89 Castlereagh Street, Sydney, Australia

MEZHDUNARODNAYA KNIGA, Kuznetskii Most 18, Moscow, U S S R

DOMESTIC AGENCIES

G E STECHERT & CO , 31 E 10th Street, New York City

ARTHUR W ISCA, 210 South Seventh Street, Minneapolis, Minn

J W STACEY, *Medical, Scientific and Reference Books*, 236 Flood Bldg , San Francisco, Calif

CHICAGO MEDICAL BOOK COMPANY, *Medical Booksellers, Publishers and Importers*, Congress and Honore Streets, Chicago, Ill

TECHNICAL BOOK CO , Underwood Bldg , 525 Market St , San Francisco, Calif

T H McKENNA, 124 East 60th Street, New York City, N Y

B WESTERMANN & CO , 13 West 46th Street, New York City, N Y

MEDICINE

All correspondence relating to the publication of papers should be addressed to the Associate Editor, Doctor Alan Chesney, The Johns Hopkins Hospital, Baltimore, Maryland

Twenty-five reprints, without covers, of articles will be furnished to contributors free of cost Additional reprints, not to exceed 175, may be purchased The Editors and Publishers feel that a large distribution of reprints would interfere with the distribution of MEDICINE When there is a special demand for a particular article, the Publishers endeavor to make such an article available in the series of books known as MEDICINE MONOGRAPHS

Correspondence concerning business matters should be sent to The Williams & Wilkins Company, Publishers of Scientific Books and Periodicals, Mt Royal and Guilford Avenues, Baltimore, Maryland, U S A

The periodical is issued quarterly A volume consists of 500 pages (4 issues of about 125 pages to the issue)

Subscription price Current Volume $5 00, United States and countries within the postal union, $5 50 countries outside the postal union Single copies will be supplied, when available, at the rate of $1 50 a copy

Claims for copies lost in the mails must be made within 30 days (domestic subscribers), 90 days (foreign subscribers) of the date of issue

Changes of address must be received at least two weeks prior to the date of issue

New subscriptions and renewals are entered to begin with the first issue of the current volume Should any issue of the current volume be out of print at the time the subscription order is received, the pro-rata value of such numbers will be credited to the next volume, and the renewal invoice therefore adjusted accordingly

Subscriptions should be renewed promptly—To avoid a break in your series, subscriptions should be renewed promptly The publishers cannot guarantee to supply back issues on belated renewals

Subscriptions, new or renewal, should be sent to the Publishers or to Agents listed below

AGENTS

For Argentina and Uruguay Beutelspacher y Cia, Sarmiento 815 Buenos Aires

For Australia Angus & Robertson, Limited, 89–95 Castlereagh Street, Sydney

For Belgium Henri Lamertin, 58 Rue Coudenberg, Bruxelles.

For the British Empire, except Australia and Canada Baillière, Tindall & Cox, 8 Henrietta St, Covent Garden, WC 2, London, England

For Canada Wm Dawson & Sons, Ltd, 91 Queen Street East, Toronto

For China Commercial Press Ltd, Paoshan Road, Shanghai, China

For Denmark H Hagerup's Boghandel, Gothersgade 30, Kjöbenhavn.

For France Emile Bougault, 48 Rue des Ecoles, Paris

For Germany B Westermann Co, Inc, Zimmerstrasse 35–41, Berlin SW 68, Germany

For Holland Scheltema & Holkema, Rokin 74–76 Amsterdam

For Japan and Korea Maruzen Company, Ltd (Maruzen Kabushiki Kaisha), 6 Nihonbashi Tori Nichome, Tokyo, Fukuoka, Osaka, Kyoto, and Sendai, Japan

For Spain Ruiz Hermanos, Plaza de Santa Ana, 13, Madrid

THE WILLIAMS & WILKINS COMPANY

Publishers of Scientific Books and Periodicals

BALTIMORE, U S A

Entered as second class matter at the Post Office at Baltimore Maryland, under the Act of March 3, 1879

THE SYPHILITIC OPTIC ATROPHIES

With Especial Reference to Primary Optic Atrophy

JOSEPH EARLY MOORE, M D

From the Syphilis Division of the Medical Clinic, the Johns Hopkins Hospital, Baltimore

Knowledge concerning the optic neuropathies due to syphilis is in a very confused state in the minds of ophthalmologists, neurologists and syphilologists alike This confusion involves the clinical differentiation of the various forms of optic atrophy, the etiology and pathology of primary atrophy, the results of treatment, and even the propriety of treating at all As in many other instances in medicine, the practical therapeutist has been in the forefront of the argument Through his efforts, something of clarity is beginning to emerge as to the major problem of treatment results, stimulated by his partial successes and his failures, much study is being devoted, especially in Germany, to the equally important questions of etiology and pathology It seems profitable, therefore, prior to a study of our own material of 200 or more cases of optic atrophy, to review the more important papers of the recent literature

CLASSIFICATION OF THE OPTIC NEUROPATHIES AND THE IMPORTANCE OF SYPHILIS AS AN ETIOLOGIC FACTOR

Woods and Dunn (1923) provide a simple ophthalmologic classification of the optic neuropathies as follows (1) primary atrophy, involving the entire nerve, without visible ophthalmoscopic evidence of any preceding inflammatory process, (2) secondary atrophy, including all cases with visible ophthalmoscopic evidence of preceding inflammation, i e , obscuration of the physiologic cup, blurring of the lamina cribrosa, or deposition of connective tissue in the cup or on the nerve head, (3) retrobulbar neuritis, showing clinically diminished central vision with a normal fundus and nerve head on ophthalmoscopic examination, and having normal field outlines for form, or

concentric contraction with the presence of central scotomas for either form or color, (4) atrophy especially localized in the papillo-macular bundle, with the clinical picture of pallor of the temporal section of the nerve, diminished central vision and normal field outlines for form but central scotomas for either form or color (this form of atrophy may often be regarded as the end result of retrobulbar neuritis), and (5) papillo-edema, including such entities as optic neuritis or neuroretinitis clearly on an inflammatory basis, or choked disc due to increased intracranial pressure Though this classification seems an easily workable one, it may be extremely difficult, even with the most careful ophthalmologic examination, to differentiate between the first four of these five groups

Each of these optic neuropathies may be caused by a variety of etiologic factors, of which syphilis, though numerically the most important, is only one In order to determine the cause, a painstaking general study of the patient must include, in addition to a detailed ophthalmologic survey, a complete physical and neurologic examination, special laryngologic study, antero-posterior and lateral stereoscopic roentgenograms of the head, blood Wassermann test, and examination of the cerebro-spinal fluid In a series of 86 patients thus studied, gathered from the material of a large out-patient department of ophthalmology, Woods and Dunn found syphilis to be responsible for each of the types of optic neuropathy described, in the proportions shown in table 1, and to be the cause of the disturbance in 40 per cent of the patients studied Twenty-five of the thirty-five instances of primary optic atrophy, or 71 per cent, were due to syphilis Woods and Dunn illustrate the improvement in modern methods of diagnosis of syphilis by quoting an older similar study by Derby (1902), who found only 7 3 per cent of 108 cases of optic atrophy to be due to syphilis, while 67 per cent were of undetermined origin

In a more recent report, Woods and Rowland (1931) have again reviewed the question of the etiology of the optic neuropathies This second paper is based on a study of 137 patients hospitalized and studied in the wards of the Wilmer Ophthalmological Institute, and contrasts with the report of Woods and Dunn, which utilized a material of ambulatory patients The incidence of syphilis as an etiologic factor is much lower in the second than in the first series, i e , 16 7 as

compared with 40 per cent Increased intracranial pressure, due to brain tumor, pseudo-tumor, or intracranial aneurysm, however, increased in incidence from 11 6 to 34 3 per cent The difference in percentage in these two groups is more apparent than real, and certainly depends on the fact that patients suspected of brain tumor are more seriously ill, and therefore better studied in the hospital than in the out-patient clinic Even under these conditions, 20 of 48 patients with *primary* optic atrophy, or 41 per cent, were found to be suffering from central nervous system syphilis

The incidence of syphilis in the causation of the various forms of optic atrophy may be roughly approximated by averaging the re-

TABLE 1

The etiologic classification of optic neuropathies (*Woods and Dunn*)

	TOTAL	CENTRAL NERVOUS SYSTEM SYPHILIS	SINUSITIS	BRAIN TUMOR	MULTIPLE SCLEROSIS	TOXIC AMBLYOPIA	SCATTERING	UNKNOWN
Primary atrophies	35	25	0	0	1	4	0	5
Papillomacular atrophies	24	4	5	1	4	5	1	3
Secondary atrophies	13	2	2	4	0	0	1	4
Optic neuritis	5	3	0	0	0	1	1	0
Choked disk	4	0	0	4	0	0	0	0
Retrobulbar neuritis	5	1	4	1	0	0	0	0
Totals	86	35	11	10	5	10	3	12
Per cent		40	12 7	11 6	5 8	11 6	3 5	13 8

sults of Woods and Dunn and of Woods and Rowland, as shown in table 2 It is at once apparent that primary atrophy is by far the most frequent type of optic neuropathy due to syphilis, and further that neurosyphilis is a more frequent cause of primary atrophy than all other etiologic factors combined

A much less detailed but nevertheless important study showing the incidence of syphilis as a cause of optic atrophy is that of Harman (1922) Among about 4000 cases of blindness from all causes, he found in 65 blind infants 7 instances of optic atrophy, none of which were due to syphilis However, optic atrophy accounted for 355 of 1855 instances of blindness among children of school age, and Harman

says that no less than 230, or 65 per cent, of these optic atrophies, were due to congenital syphilis, most of which were associated with extensive disseminated choroiditis It is a little difficult, in view of the careful studies by Woods and his collaborators, to believe the accuracy of Harman's statement that of 270 optic atrophies found in 925 blind adults, only 26, or 10 per cent, were due to syphilis

The papers of Woods and his associates certainly represent the most careful recent study of the etiologic factors underlying the optic atrophies since the introduction of modern diagnostic measures, and the overwhelming importance they ascribe to syphilis as a cause of the lesion emphasizes the necessity for study of the syphilitic atrophies

TABLE 2

The etiologic classification of the optic neuropathies (combining the series of Woods and Dunn and of Woods and Rowland)

	TOTAL CASES	CENTRAL NERVOUS SYSTEM SYPHILIS	ALL OTHER CAUSES	PERCENTAGE INCIDENCE OF NEURO-SYPHILIS
Primary atrophies	83	45	38	54 2
Secondary atrophies	25	3	22	12 0
Retrobulbar neuritis	18	1	17	5 5
Papillomacular atrophies	47	5	42	10 6
Papilledema	50	4	46	8 0
Total .	223	58	165	26 0

Igersheimer (1918) points out that syphilis may produce atrophy of the optic nerve in a variety of ways (1) Atrophy may occur in association with disease of the bulb, especially the severe choroido-retinitis of congenital syphilis, or the severe intraocular inflammatory conditions of acquired syphilis In such cases, it may be very difficult to decide whether the atrophic process in the nerve is secondary to, or merely simultaneous with, the intraocular condition Jonas Friedenwald and the author have recently seen a tabetic with a severe choroido-retinitis and an apparent pigmentary degeneration of the retina associated with primary optic atrophy (2) Atrophy may occur in gumma or periostitis of the orbit, due to direct pressure upon and resulting nutritional disturbances in the intraorbital portion of the optic nerve (3) Atrophy may occur in patients presenting the

neurologic picture of basilar syphilitic meningitis Here the atrophy may be secondary, as the end result of papillitis, or apparently typically primary If the latter, Igersheimer thinks (and a study of our own clinical material will subsequently afford confirmatory evidence) that it may be a matter of extraordinary difficulty to distinguish between primary atrophy due to tabes or to basilar meningitis He points out that it is not uncommon for optic atrophy to be almost the only sign of neurosyphilis, and that positive findings in blood or spinal fluid do no more than to establish the diagnosis of neurosyphilis, not to differentiate its type He believes that the diagnosis can often be made on the basis of collateral neurologic signs, or sometimes on the results of treatment, since he appears to feel that treatment is more hopeful in the atrophy due to basilar meningitis than in that due to tabes [1] (4) Atrophy may be due to the pressure of syphilitic inflammatory products on the cerebral optic conduction apparatus anywhere from the orbit to the corpora geniculata externa Igersheimer mentions as examples, pressure on the chiasm or the intracranial portion of the optic nerves by atheromatous vessels, gummas of the hypophysis, or hydrocephalus of the third ventricle If there are atheromatous changes in the cerebral vessels on a syphilitic basis, the atrophy may be as much due to nutritional disturbances of the nerve as to pressure Igersheimer cites a single case of Behr's, and mentions that Wilbrand and Saenger have seen similar instances, in which optic atrophy was apparently due to the pressure of syphilitic plaques in cerebral vessels on the nerve stalk It is difficult to see, however, how one could differentiate clinically between atheroma of the vessels, or its effect on the optic nerves, due to syphilis or to the more frequent cerebral arteriosclerosis (5) Finally one finds the genuine optic atrophy of tabes dorsalis, tabo-paresis and general paresis

[1] It is not uncommon to meet with the ophthalmologic criticism that if a given patient with optic atrophy improves, the atrophy could not have been primary (*Uhthoff*, in discussion of Greef's paper, 1922) This reminds one of the premalaria days of the treatment of paresis, when, if a paretic patient recovered under any form of treatment, some one could always be found to dispute the diagnosis of paresis Once the idea has become fixed in the minds of physicians that a certain disease is incurable, it is almost impossible to overcome it unless by such overwhelming evidence as was provided by insulin, liver or malaria Since no such evidence is as yet available for syphilitic primary optic atrophy, its supposed refractoriness to treatment is often wrongly included as a criterion of diagnosis On the basis of our own experience, I do not believe it justifiable to assume that optic atrophy is due to basilar meningitis if the patient improves, or to tabes if he does not

Since the primary optic atrophy associated with parenchymatous neurosyphilis (tabes and paresis) is by far the most frequent of these types and is also that about which there is most confusion, particular attention will be devoted to it

THE FREQUENCY OF PRIMARY OPTIC ATROPHY IN NEUROSYPHILIS

Igersheimer's book provides a detailed review of the literature prior to 1918 and gives, on the basis of his own experience and that of others, numerous figures as to the frequency of optic atrophy in tabes He estimates that from 10 to 15 per cent of all tabetics ultimately develop primary optic atrophy He points out that while optic atrophy also occurs in paresis, it is much more frequent when the disease picture is of the tabo-paretic type than when the symptoms are purely cerebral Wagner-Jauregg (1927) goes further than this and thinks that optic atrophy in paresis is very rare unless there are associated manifestations of tabes In juvenile (congenital) tabes and paresis, Igersheimer says that optic atrophy occurs in about 50 per cent of the reported cases, though in many of these instances he thinks there may have been an associated cerebrospinal (mesoblastic) neurosyphilis as well as meta- (parenchymatous) syphilis

The magnitude of the problem of primary optic atrophy is easily emphasized by the consideration of a few well-known statistics The most reliable recent estimate of the incidence of syphilis in the general population of this country is that of Usilton (1930), based on actual surveys directed by the United States Public Health Service She estimates that there are 423,000 new infections with syphilis each year From these figures and the census reports of the numbers of the population of different age groups, it seems probable that at least 10 per cent of the adult population is infected Of untreated or badly treated syphilitics, approximately 5 per cent develop tabes dorsalis (Mattauschek and Pilcz, 1913) Leaving out of consideration the question as to whether more modern treatment methods than those discussed by Mattauschek and Pilcz have done anything at all to decrease the incidence of neurosyphilis—and this is a subject which is as yet unsettled and on which there is violent debate pro and con—there must at any one time be more than half a million sufferers from tabes in the United States If 10 to 15 per cent of these may be ex-

pected to develop optic atrophy, about 50,000 cases of this condition are constantly present Since heretofore the expectation has been that all such patients progress inexorably to complete blindness, the economic importance of the question, to say nothing of its urgent and vital importance to the individual patient, is obvious

Incidentally, it is worth noting that, according to John (1929), who has studied the admission diagnoses in a large ophthalmologic clinic, there has been no increase in syphilitic primary optic atrophy over the 20 year period 1905–1925 Whatever modern treatment methods of early syphilis may be doing to increase the incidence of other types of neurosyphilis, there is thus no evidence that it has had any effect on the incidence of optic atrophy

It seems to be assumed by many ophthalmologists and neurologists, particularly of the older school, that if the patient has primary optic atrophy, the neurosyphilitic process must be tabetic in type This assumption is no doubt due to the often made clinical observation, discussed by Igersheimer, that atrophy often appears as the earliest manifestations of tabes, in the so called pre-ataxic stage He cites the experience of Galezowski, who saw 55 cases of optic atrophy in the pre-ataxic stage of tabes, and only 8 in whom the atrophy developed after ataxia had appeared Others, also quoted by Igersheimer, have even taken the extreme view that optic atrophy and the posterior column symptoms of tabes are mutually antagonistic, i e , that the development of optic atrophy is more or less of a guarantee against the subsequent appearance of incapacitating posterior column symptoms and vice versa However this may be, it is certainly true that one often sees primary optic atrophy as one of the earliest signs of tabes, that in such cases it may be many years before the appearance of the typical cord symptoms, and that in patients in whom severe cord symptoms are an early feature, optic atrophy is relatively unlikely to develop If a tabetic with optic atrophy has or subsequently develops cord symptoms, the latter often progress very slowly, or come to an early and spontaneous standstill

Igersheimer is willing to make the diagnosis of tabes on the basis of pupillary changes alone, especially anisocoria and the Argyll-Robertson phenomenon, and many other ophthalmologists and neurologists are apparently willing to diagnose tabetic optic atrophy in the com-

plete absence of cord symptoms, with the idea in mind that such patients are in the pre-ataxic stage of tabes and will develop cord symptoms later Others regard such patients as instances of optic atrophy due to basilar meningitis On the basis of our own experience, we have become convinced that there is a large and important group of patients with primary optic atrophy due to neurosyphilis where the only neurologic abnormalities present are the atrophy and pupillary changes, that these patients cannot be diagnosed either as tabes or as basilar syphilitic meningitis, on clinical grounds or on the basis of laboratory evidence, and that the subsequent course of events does not aid in the diagnosis, because no other neurological lesions, and particularly no evidence of involvement of the posterior columns, may develop during many years of observation This feeling is shared by Hawthorne (1922), who also raises the issue as to whether all cases of syphilitic primary optic atrophy are tabetic He concludes, on clinical grounds only, that the process in the optic nerves is essentially the same whether or not evidence of posterior column involvement is, or ever becomes, apparent This important question of the relationship of optic atrophy to types of neurosyphilitic involvement of the nervous system will be discussed subsequently, in connection with the pathologic anatomy of the optic neuropathies

THE OPHTHALMOLOGIC DIAGNOSIS OF PRIMARY OPTIC ATROPHY

The best discussion of this question is provided by Igersheimer (1918) Primary optic atrophy due to syphilis is practically always bilateral, though one eye may be involved weeks, months, or even a year or two before the other Unilateral involvement with the maintenance of normal visual acuity, field, and fundus on the other side over a period of years is extremely unusual, and Uhthoff (quoted by Igersheimer) saw only one such patient in a series of 300 tabetic atrophies The ophthalmoscopic picture of atrophy is often discovered before the patient has had any symptoms of visual failure The pallor of the disc usually involves the whole disc uniformly, though in early cases it may affect the temporal halves only Secondary atrophy, with evidences of a pre-existing inflammatory process in the disc, is extremely rare, and likewise in primary atrophy there are rarely associated intraocular changes of co-existent or pre-existing in-

flammatory lesions It is a curious fact that among the many patients who develop iritis, keratitis, choroiditis or choroido-retinitis, or even neuroretinitis as a part of early secondary or relapsing secondary syphilis, outspoken primary optic atrophy seldom develops subsequently The retinal vessels show only slight alteration, if any, in the early stages, and later there is usually only a moderate amount of contraction, especially of the arteries

It is a point of great importance, both in diagnosis and treatment, that the ophthalmoscopic picture of pallor of the optic discs does not always parallel the degree of visual impairment This fact has impressed us more than once in our own material and has also been discussed by others Traquair (1922) points out that it is often difficult to decide whether optic atrophy is or is not present, and that the diagnosis must sometimes rest on the skill and experience of the individual observer He illustrates the lack of parallelism between pallor of the disc and visual impairment by citing the fact that in descending atrophies of the nerve from pressure or from disseminated sclerosis, visual loss often far exceeds the degree of pallor, while in early tabetic optic atrophy or in retrobulbar neuritis after recovery, the reverse may be true Traquair thinks, quite correctly, that careful studies of the visual fields are indispensable in attempting to estimate the anatomic and physiologic damage Dworjetz (1928) reports 9 patients who showed ophthalmoscopically apparent "total atrophy" of the discs but in whom visual acuity was absolutely normal In practically all these patients, the visual fields for form were moderately to markedly concentrically constricted The clinical picture from the ophthalmoscopic standpoint was primary atrophy in five, neuritic atrophy in three, and secondary atrophy after choked disc in one The cause of the process is given as tabes in one, cerebrospinal syphilis in two, multiple sclerosis and sinusitis one each, and typhoid fever and methyl alcohol poisoning two each Unfortunately, there are no data as to whether these patients subsequently developed any visual failure

Dworjetz concludes that while cases with "porcelain white" discs without the slightest red color, but with completely normal vision, are rare, they do occur, and that it is not possible always to diagnose optic atrophy from the color of the discs, which does not always ex-

press the functional state of the nerve, nor is the color necessarily related to the number of degenerated nerve fibres present in an atrophic nerve

In this connection, a recent paper by Somberg (1927) is of interest This observer was associated with the Manhattan State Hospital where he states that he had the opportunity to examine the eyes of about 2000 paretic patients before and during treatment with tryparsamide He found 86 patients who had pallor of the optic discs before treatment, the color ranging from pale orange to white Seventy-three of the 86 had normal visual acuity (data as to visual fields not mentioned), while 13 had some loss of vision, but never less than 20/40, with practically normal fields During a period of two years' observation, vision was reduced in 46 of these patients In 22 it fell to 20/200 (or less?) with marked concentric constriction of the visual fields, and this visual failure often occurred suddenly, within a period of 2 to 3 weeks In 24 others, vision diminished to a point between 20/50 and 20/100, without much alteration of the fields The author regards this as evidence of progress in optic atrophy due to syphilis Unfortunately his conclusion is based on uncritical reasoning, since he fails to state whether tryparsamide, a drug known to produce damage to the optic nerve (Woods and Moore, 1924), was used in these 86 cases, or whether similar visual loss, with or without the appearance of pallor of the discs, occurred in the remainder of the 2000 paretics, some of whom were and some were presumably not, treated with tryparsamide The sudden occurrence of visual failure suggests that it may have been due to tryparsamide rather than to syphilis

To continue with Igersheimer's description of the clinical aspects of primary optic atrophy, he points out that the associated changes in the visual fields are of the utmost importance for diagnosis because, in all probability, alterations appear in them before any change is apparent in the color of the discs The first evidence of trouble is usually constriction of the fields for white and color, while normal central vision is retained This constriction may be concentric, wholly irregular in outline, or it may take out one or another sector of the visual field In the latter case the color fields show the same sector defects as the form fields Frequently the constriction begins from above

downward There may be constriction of the color fields while the form fields remain normal Igersheimer says that colors are progressively lost in the order green, red, blue, and that when green perception is entirely lost the whole optic nerve is already involved Enlargment of the blind spot is an early symptom Scotomas, central or otherwise, are very rare Igersheimer quotes Uhthoff as having seen them in 2 per cent of patients with tabetic primary optic atrophy, though always in association with peripheral field changes Igersheimer himself and others also have, however, seen scotomas with normal peripheral fields in undoubted cases of tabes Hemianopsias, binasal or bitemporal, also occur very rarely, though, as Igersheimer points out, these may be only a pseudo hemianopsias due to symmetrical defects in the peripheral fields As a matter of fact, the great rarity of hemianopsias in tabetic atrophies is, as will be subsequently mentioned again, a strong argument in favor of the fact that the primary pathologic lesion is in the optic nerve anterior to the chiasm

Behr in numerous publications has laid great stress on disturbances of dark adaptation as an early, perhaps the earliest, diagnostic sign of tabetic primary optic atrophy His opinions are strengthened by the confirmatory experience of Schindler (1922) The physiologic mechanism involved in dark adaptation, and practical methods for testing it, are reviewed in detail in a recent monograph by Adams (1930), and need not be described here Much of the work on dark adaptation in syphilitic primary optic atrophy and in neurosyphilis generally, must be critically repeated, however, since Igersheimer (1928) among others has shown (1) that not all eyes with atrophic nerves show any disturbance of dark adaptation, and (2) that there is a fairly large group of tabetics with adaptation changes but no other evidence of damage to the optic nerve, that these changes apparently depend on the presence of disturbances in the pupillary light reaction, especially if the pupil is miotic, and that they disappear when the pupil is dilated by mydriatics

From the clinical standpoint, the elucidation of many of the unsolved problems of optic atrophy requires a close working liaison between syphilologist and ophthalmologist As will be subsequently shown, the success or failure of treatment depends very largely on the question of early and accurate diagnosis of optic atrophy In this

connection it is important to note that while ophthalmologists generally feel that visual field changes probably precede visual failure or pallor of the disc, nothing is known of the incidence of visual field defects in neurosyphilitics without loss of visual acuity and with normal discs Certainly no detailed studies have been published since the introduction of modern instruments of precision for field taking Igersheimer has examined routinely a large number of paretics and tabetics, and has found many (proportion not stated) with constriction of the visual fields Unfortunately, he has been unable to follow such patients. and is unable to state whether such field defects always

public on opticians and optometrists, rather than on ophthalmologists, often leads to the unfortunate result that by the time the patient reaches competent medical attention, he has already passed through a half dozen pairs of hands, has been fitted with glasses or had them changed, and vision is seriously injured The course of untreated primary optic atrophy is progressively downhill, the average duration of the process from onset of symptoms to blindness being, according to Igersheimer, 2 to 3 years, with extremes of 2 to 3 months to as long as 12 years As with other manifestations of tabes, there may be remissions of longer or shorter duration, though in our own experience this is unusual The lack of uniformity in progress, and the possibility of spontaneous remissions, makes it extremely difficult to evaluate the effects of treatment, since in the individual case, one cannot be certain that the process would not have been equally as promptly "arrested," and remained quiescent for as long a time, as if nothing had been done

THE PATHOLOGY OF OPTIC ATROPHY

Igersheimer (1928) summarizes the important questions to be answered by a study of the pathology of primary optic atrophy These are (1) In what part of the optic tract does the process begin? (2) In which portion of the optic nerve are changes first observed? (3) What relationship, if any, have inflammatory processes to the degeneration of the fibres of the nerve? (4) Are *T pallida* actually present in the lesion, and if so, what importance have they in its production?

A clear understanding of the work which has been done on the optic atrophies presupposes some knowledge of the general pathology of neurosyphilis There are various classifications of neurosyphilis on a clinico pathologic basis, one of the simplest of which, as evolved by Stokes and Shaffer (1924) and by Moore (1927) from that of Head and Fearnsides (1914), is as follows

1 Meningeal
2 Predominantly meningovascular (cerebrospinal syphilis)
3 Vascular
4 Parenchymatous
  a Tabes dorsalis
  b General paresis
  c Taboparesis

It is obvious, from both clinical and pathologic standpoints, that it is often impossible to assign an individual patient with exactness to one or another of these groups In almost all patients with clinical neurosyphilis of any type, there is evidence of some degree of meningeal, vascular, and parenchymatous involvement, and the most that one can say is that the type of involvement is predominantly meningeal or vascular, or meningo-vascular, or parenchymatous In a general way, however, the classifications mentioned may be briefly described and their association with primary optic atrophy pointed out.

(1) Meningeal neurosyphilis—acute syphilitic meningitis, neurorecurrence—is usually an early manifestation of the disease, is characterized by an exudative and inflammatory process in the meninges, and involvement of the optic nerve is frequent in the form of optic neuritis or neuroretinitis Necropsies on such patients are rare, since recovery is the rule Reports are however available, from Pette (1924) for example Treponemes have been found with relative ease and in considerable numbers in the diseased areas Fuchs (1924) reports such a case, a patient who developed a neurorecurrence with bilateral neuroretinitis, and subsequently died of acute yellow atrophy of the liver after 19 injections of silver arsphenamine At necropsy, there were no alternations in the optic nerve heads (probably healed by treatment), but in both nerves behind the eye there was a slight round cell infiltration and glial proliferation without meningeal changes Treponemes were not searched for It is particularly noteworthy, Behr states (1926), that in spite of the frequency of involvement of the optic nerves in such cases, this usually subsides (even if untreated) without the slighest visual disturbance or atrophy This is contrary to current ophthalmologic opinion, which holds that such inflammatory changes in the optic nerves usually leave some evidence of atrophy, even though slight, in their wake Behr claims to have shown that in syphilitic meningitis, degenerative changes in the optic nerves occur only when there is infiltration along the connective tissue septa and about the vessels within the nerve itself He has seen instances in which the meningeal covering of the whole optic nerve was involved in a syphilitic inflammatory process but in which the interior of the nerve was penetrated only at one point Degeneration of nerve

fibres was present at this point only, and not elsewhere According to Behr, this is conclusive evidence that degenerative and atrophic changes of the nerve are not due to the influence of meningeal infiltration or thickening of tissues about the nerves

There is also a late variety of syphilitic meningitis, in which the clinical symptoms are not so acute or fulminating as in the early variety Pathologically, as described by Le Count and Dewey (1915), for example, this consists in a discrete or diffuse gummatous infiltration of the meninges, especially about the base Clinically, the picture is diverse but is usually characterized by severe headaches, pupillary abnormalities, and often cranial nerve palsies Some examples of apparent primary optic atrophy are associated with this type of neurosyphilis

(2) The predominantly meningovascular or cerebro-spinal neurosyphilis is a catch basket classification from the clinical standpoint, including all patients who fail to fit clearly into one of the other groups From the pathologic standpoint the lesions are diffuse, often multiple, and tend to involve more or less purely the mesoblastic elements of the nervous system, the meninges and the blood vessels Since the discovery of modern staining methods for *T pallida*, such as that of Jahnel (1924), far less attention has been focused on this type of neurosyphilis than on general paresis, but treponemes can often be found, especially in the perivascular infiltrations It is questionable as to what extent primary optic atrophy is associated with this group

(3) In a relatively small group of neurosyphilitics, the involvement is almost exclusively vascular, consisting of endarteritis and periarteritis, and is manifested clinically by hemiplegias, monoplegias, aphasias —cerebral vascular accidents often indistinguishable clinically from cerebral hemorrhage or thrombosis from other causes Optic atrophy is an uncommon accompaniment of this type of lesion

(4) The two great divisions of parenchymatous neurosyphilis, tabes and paresis, differ in many important respects from other types of neurosyphilis, not the least important of which is their relative refractoriness to treatment Since the demonstration by Noguchi and Moore (1913) that treponemes could be found actually in the nerve tissues of the brain in paresis, a great deal of additional work has established the fact that not only are they present, but present in large

numbers (Jahnel) They may be found not only in the nerve tissues, but also in the meninges and about the blood vessels Their presence leads to actual destruction of brain cells, though curiously enough, their localization is usually such that the intellectual functions of the brain, rather than its motor or sensory functions, are the ones to suffer Cranial nerve paralyses are rare As already pointed out, optic atrophy is uncommon in paresis unless tabes also exists

In tabes, however, the situation is quite different The primary lesion is probably not within the central nervous system at all, but in the posterior nerve roots There is great debate, and a half dozen theories, as to the exact location of the primary lesion and the method by which it develops (Richter, Spielmeyer, Hassin, and others, summarized in a recent article by Stern (1929)) The spinal cord lesions and theories as to their origin need not detain us here. However, it is necessary to emphasize the point brought out by Stern, that in spite of many attempts to demonstrate *Treponema pallida* in the cord or root lesions of tabes, only four observers have been successful (Noguchi one case, Versé two cases, Jahnel one case, Richter 3 cases) In contrast to the rich spirochetal content of the brain in paresis, the nervous system thus seems singularly devoid of these organisms in tabes Moreover, tabes is frequently associated with four isolated cerebral disturbances first, and most frequent, the characteristic pupillary

revealed any visible lesion in this area, and that treponemes have never been demonstrated in it Even if this were not true, it would be difficult to explain the uniform selective invasion of this tiny area by organisms, especially since the neighboring nucleus of the oculomotor nerve, to say nothing of other cerebral areas, is so infrequently involved Ingvar has evolved an explanation of the pupillary changes on the basis of a widespread rather than an intensely-localized lesion He feels that in spite of the absence of definite evidence for the exact path of the pupillo-motor fibres in man, there are evolutionary and phylogenetic reasons for thinking that these pathways run on the surface of the diencephalon, and that many of the more superficial nerve fibres lack myelin sheaths Exudative and inflammatory processes at the base are, he says, to some degree universal in metasyphilis (tabes and paresis), and the inflammatory lesions in the pia and arachnoid are in direct contact with the unmyelinated nerve fibres on the surface of the cerebrum (and also with cranial nerves) This contact leads to marginal degeneration of the optic pathways with resultant injury to the pupillo motor paths Ingvar thinks that this basilar meningitis may also be the explanation of the isolated ptosis occurring in tabes from injury to the fibres supplying the levator of the lid and the superior rectus muscle, which are known to run on the margin of the third nerve, and that it may also explain the early concentric constriction of the visual fields so often observed in optic atrophy, since unmyenlinated nerve fibres are also present in the periphery of the nerve If necropsy shows no evidence of basilar meningitis in a metasyphilitic patient, Ingvar assumes that it was formerly present, and has left the various degenerative processes in its wake The difficulty with this explanation is the fact that inflammatory processes at the base are not universal in tabes, indeed, so careful an observer as Richter thinks that they are rarely extensive and that if present in considerable degree, they indicate a co existent paretic process

Spielmeyer (1923) has shown that in metasyphilis, inflammatory and degenerative changes may exist side by side in the nervous system but that they need not necessarily be parallel in degree While degenerative changes may occur as the result of inflammation they may also exist in high degree (as in tabes) without direct relation to it To explain this phenomenon, certain investigators, notably Hauptmann

(1924, 1930), see a process at work in metasyphilis not dependent on the direct consequences of the presence of *T. pallida* in the nervous system Hauptmann assumes that the nervous system is damaged by a toxin, dependent on the presence of organisms in the body outside the nervous system as well as within it This toxin, whether it is elaborated by living treponemes, whether it arises from their extra-phagocytic destruction in the host's battle against them, or whether it is a substance normally present in the blood stream which is toxic for nervous tissues but under normal circumstances is prevented from reaching them, may gain access to the nervous system by an upsetting of the normal barrier between blood and spinal fluid, and this in turn may be due to the presence of few or many organisms within the nervous system The apparent selective action of the hypothetical toxin for the pupillo-motor pathways and the optic nerve is no more difficult of explanation than the action of other and better known toxic substances, such as methyl alcohol or tryparsamide It is impossible in a short space to give the detailed steps of Hauptmann's reasoning, one can only say that his theory explains many of the clinical and pathologic facts of metasyphilis which otherwise appear inexplicable with our present knowledge

Stimulated by these and other considerations, Behr (1926) concludes that neurosyphilis may be still more simply classified into three main groups (1) mesodermal neurosyphilis, involving brain or spinal cord (and including the meningeal, vascular, and meningo-vascular groups above), (2) ectodermal neurosyphilis—general paresis, and (3) metasyphilis—tabes dorsalis He postulates that in the first two of these groups, the damage is done by the actual presence of *T pallida* in mesodermal or ectodermal tissues, in the third, the lesions are dependent on the hypothetical toxic, as well as on specific, influences

The modern study of the pathologic anatomy of primary optic atrophy begins with Stargardt (1913) Many earlier authors had held that the degenerative changes in the nerve were dependent on changes in the ganglion cells and nerve endings in the retina Stargardt studied the visual apparatus of 19 patients with paresis, 4 with tabo-paresis, and 3 with tabes Six of these (2 paretics, 3 tabo-paretics, and 1 tabetic) showed advanced optic atrophy, in four others, all paretics, there was outspoken partial atrophy The findings did

not differ materially in paretics and tabetics The first and earliest evidence of damage to the visual pathways was in the chiasm, and consisted in an undue proliferation of glia fibres, with isolated plasma cells in the overlying pia Next the intracranial portion of the optic nerves was similarly involved With increasing infiltration of round and plasma cells in the covering pia, there was a simultaneous proliferation of glia fibres in the nerve As time went on, the medullary sheaths underlying the infiltrated areas showed degeneration, and later the axis cylinders and fibrillae were also involved, to be finally replaced by glia cells filled with amyloid The intraneural connective tissues and blood vessels showed no early alterations, and could be apparently normal even in far-advanced atrophy

Stargardt states that in the 8 of his 26 patients who showed no degeneration in the optic nerves or chiasm, exudative changes in the covering pia were almost or wholly absent However, as Wagner-Jauregg points out, exudative changes in the meninges of paretics, who composed the majority of Stargardt's material, are almost universal, and their presence or absence can be of little real importance for the development of optic atrophy

Palich-Szanto (1917) studied 9 cases of optic atrophy, and agreed that exudative changes were present in the overlying membranes of the intracranial portion of the optic nerve, and the chiasm and that the degenerative changes were most marked in the periphery of the optic nerves Here the nerve tissues were almost wholly replaced by glia fibres The optic tracts and the geniculate bodies were wholly free from lesions This observer made an extended search for treponemes, without success

In Richter's (1912) three cases of optic atrophy in uncomplicated tabes, the findings were essentially the same as in Stargardt's patients Richter agrees with Stargardt that the atrophic process in the nerves is the same in paresis as in tabes

Fujiwara (1925) studied the visual pathways in 19 neurosyphilitics, of whom 10 had tabes, 2 probable tabes, 1 questionable tabes, 2 taboparesis, and 4 pupillary changes only Clinical data as to visual acuity and the ophthalmoscopic picture were lacking in 5, in 12, vision and fundi were normal, and optic atrophy was present in two patients From the pathologic standpoint, all patients except two showed some

degree of atrophy of nerve fibres in the intracranial portion of the optic nerve, even including 9 patients with perfectly normal fundi during life Some degree of atrophy was present in the chiasm in 11 cases, while in the tracts (investigated in 14 patients only), there were atrophic changes in 3 instances, including the two patients with optic atrophy, cellular infiltration of the overlying pia was found in all cases except two The predominating cell was the lymphocyte, plasma cells were few The degree of infiltration was variable but was regarded as moderate in all Perivascular infiltration of the vessels running in the connective tissue septa of the nerve was present in 5 patients Treponemes were not found in pia or nerve tissues in 11 cases studied These findings are obviously contradictory of the earlier study of Stargardt

Behr has been a deep, if very pessimistic, student of the question of primary optic atrophy He examined (1926) serial sections, from the eye to the geniculate bodies, of 9 cases of optic atrophy He concludes that the degeneration always begins at the nerve margins, in the nerve bundles underlying the pia It may occur in a single area or in several simultaneously, and may progress at different rates He believes that it always occurs distal to the chiasm, partly because of the great rarity of hemianopsia during life, partly because he has seen cases with moderately advanced atrophy of the optic nerves with only slight changes in and behind the chiasm The intracranial portion of the optic nerve is, according to Behr, the portion of the visual pathways in most intimate contact with the pia and the mesodermal connective tissue septa Exudative changes in these mesodermal tissues are constantly demonstrable in tabetic optic atrophy and absent in all other atrophic processes in the nerves The primary change in syphilitic primary optic atrophy, Behr believes, is an inflammatory process in the connective tissue septa of the intracranial portion of the nerve and of the blood vessels which run within them Such changes are demonstrable both early and late in the process These changes, especially those of the blood vessels, impair the nutrition of the nerve fibres and degeneration results Exudative processes in the meninges are, according to Behr, merely coincidental, as shown by their inconsistency There are numerous instances of marked infiltration of the pia overlying chiasm and nerves, with no evidence of optic

atrophy, and conversely, many instances of optic atrophy in the absence of such changes Behr agrees with Richter that exudative meningeal changes at the base are rare in tabes, and that if present, they raise the question of a co-existing paretic process

It seems to Behr important, and not elsewhere much stressed, that in early cases of optic atrophy the medullary sheaths are first affected, involvement of the axis cylinders coming later He feels that this is the explanation for the fact that one can see the ophthalmoscopic picture of optic atrophy without any visual change except in the phenomenon of dark adaptation

Behr believes with Hauptmann that a toxin of some sort must be partly responsible for optic atrophy, but does not agree that its effect is on the nerve fibres He eliminates them partly because the apparent constant association of exudative changes in the mesodermal septa and vessels with degeneration of the nerve fibres is so unsystematic Here and there throughout the central, intermediate, or subseptal portions of the nerve, one finds degenerated fibres surrounded by and in contact with others which are quite normal If therefore the atrophic process is dependent on a toxin, some other portion of the nerve than the nerve fibres themselves must be susceptible to the toxin, namely, the glia fibres In Behr's opinion the glia fibre system is the lymph supply system of the optic bundle and the nerve fibres are nourished through it Morphologic and physico-chemical alterations in the glia fibre system result in a disturbance of nutrition in the nerve fibres and their medullary sheaths If the nutritional disturbance is prolonged, death results, first of the myelinated sheaths, then of the axis cylinders The primary change is, he thinks, not only in the marginal but also in the parenchymatous glia fibres, the secondary result is a disturbance of nutrition of the nerve fibres, ending in degeneration

Igersheimer (1926, 1928) points out that on the basis of his own and earlier pathologic studies there is general agreement as to the facts that atrophy begins in the intracranial portion of the optic nerve distal to the chiasm, and that the degenerative process occurs first in the marginal fibres of the nerve He states that there is as yet no agreement as to the third question of importance, i e , the relationship of the degenerative to inflammatory processes His own studies of the

visual pathways of a large number of paretics, tabo-paretics and tabetics with and without optic atrophy, clarify this situation only in a negative sense He found that round and plasma cell infiltration of the pia and arachnoid, near and around the chiasm and in the intracranial portion of the optic nerve, was frequent in both paresis and tabes, and this whether optic atrophy was present or absent He regards it as important that in one case in which he could follow a beginning atrophy through the whole visual tract, there was only a very minimal cellular infiltration of the pia and none at all in the septa of the nerve

Igersheimer has also provided the first reliable evidence as to the potential rôle of the actual presence of *T pallida* in the causation of optic atrophy Among 40 neurosyphilitics, the optic nerves were quite normal in 10 (7 paretics, 3 tabetics) and in one of these patients only, he found a single *T pallidum* in the optic tracts within the brain In 9 cases (8 paretics, 1 tabetic), there were marked inflammatory changes in the pia about the chiasm and nerves and in the septa, but no demonstrable degenerative lesions Treponemes were demonstrated in the pia and arachnoid of the intracranial portion of the optic nerve in three of these patients (all paretics) and in one of the three also in the septa and glia Optic atrophy was present in 21 patients (11 paretics, 4 tabo-paretics, 6 tabetics) Treponemes were demonstrated in 7 of these (once by dark field) in various parts of the visual apparatus, ranging from the meningeal coat of the intracranial portion of the optic nerve to the external geniculate body In all, Igersheimer found the organisms in the visual apparatus (but never in the nerve tissues proper) of 1 of 10 tabetics, 2 of 4 tabo-paretics, and 7 of 33 paretics To put it differently, treponemes were present in 3 of 9 patients with inflammatory but no degenerative changes, and in 7 of 21 patients with definite atrophy, or in exactly the same proportion whether optic atrophy was present or absent

Pacheco e Silva and Candido da Silva (1929), in a paper which is accessible to me only in abstract, report that they studied the intracranial portion of the optic nerves of 21 paretics by Jahnel's technic Unfortunately, the abstract does not state whether any of these patients had optic atrophy In one case, many treponemes were found, within the nerve substance

The net result of these elaborate pathologic studies by various competent observers has been to settle only the question of the point of origin of optic atrophy in the marginal fibres of the intracranial portion of the optic nerve distal to the chiasm It seems obvious from what has been said that the atrophic process bears no direct relationship to the presence or absence of exudative changes in the overlying or neighboring meninges or to the presence or absence of *T pallida*, in or close to the visual pathways

After a consideration of these same data, Wagner-Jauregg criticizes the pathologic evidence by saying that a study of the visual apparatus in uncomplicated paresis (on which a good deal of the work has been done) is of no particular value for elucidating the problem of optic atrophy, even in tabo paresis with optic atrophy the extensive pathologic changes in the whole brain render unsafe any conclusions as to such a highly specialized part of the brain as the visual tracts What is needed is a study of pure tabes with optic atrophy, and most important of all, with beginning atrophy This is obviously very difficult, since such cases rarely come to necropsy He adds that any theory of the development of optic atrophy must fit this particular process to the pathologic and clinical entity of tabes dorsalis, and must explain such clinical facts as the frequent preataxic occurrence of optic atrophy, and its development in occasional cases of otherwise apparently stationary tabes, with negative serology of blood and spinal fluid

The apparent lack of relationship between the presence of *T pallida* in or around the optic nerves and the occurrence of optic atrophy has been one of the strong points of Hauptmann's toxin theory, and has also been advanced as a possible explanation for the relative inefficiency of anti-syphilitic treatment Here again the evidence provided by the practical therapeutist is of some value It will be presently shown in the section dealing with treatment that there are two forms of therapy which are sometimes successful in bringing about arrest or even slight improvement in the atrophic processes, namely, the subdural injection of various medicaments, and fever therapy If optic atrophy is due to Hauptmann's hypothetical toxin, it seems reasonable to assume that the degenerative process will continue so long as the toxin continues to reach the optic nerves Routine antisyphilitic

treatment, judging by its failure to impede the downhill progress of optic atrophy, is not wholly successful in eliminating the toxin It seems unlikely that the addition to routine treatment of such procedures as the intraspinal or intracisternal injection of neoarsphenamine, mercury, air, or arsphenaminized serum would cause a cessation of production of the toxin, which Hauptmann postulates is elaborated outside the nervous system rather than within it On the other hand it is much more probable that the favorable result of the direct contact of medicated substances with diseased tissue means the destruction of living organisms responsible for the disease process If this be true, it is necessary first to explain the presence of treponemes in optic nerves of neurosyphilitics without optic atrophy, and second, their apparent absence in many cases when optic atrophy exists As to the former, it is of course well known that the tissue response to the presence of the *T pallidum* in the nervous system is an exceedingly slow and chronic one, and that, for example, although the neuraxis is invaded by organisms within the first year of infection, the tissue response resulting in neurosyphilis develops so gradually that 2 to 25 years elapse before the appearance of symptoms It is quite conceivable, therefore, that had the individual with treponemes present in a normal optic nerve lived longer, optic atrophy might have developed

As to the latter, it has been frequently suggested that the spiral form of the *T pallidum*, so well known to us, is only one phase in the life cycle of the organisms, and that the cycle may also include granular

the hypothesis that these granules represent the infective stage of the organism and a part of its reproductive cycle, but regard this as at least possible Should further investigation establish the proof of this hypothesis, it seems probable that optic atrophy, as well as other lesions of neurosyphilis of obscure etiology, may be due to the direct invasion of the tissues by the variant form of the organism This would also explain the beneficial effect of subdural therapy in optic atrophy and in certain other lesions of tabes

One other aspect of treatment is perhaps of importance in the argument as to whether optic atrophy may be due to the actual presence of living organisms (in whatever stage of their reproductive cycle) in or around the optic nerves This is the frequently repeated clinical observation that in some cases, treatment started with an arsphenamine product or with malaria results in prompt acceleration of the rate of visual failure This has been emphasized by Behr, as one argument against all forms of treatment From the clinician's standpoint, this would appear to be a typical Jarisch-Herxheimer reaction, entirely analogous to similar reactions in other tissues of the body, and thought to be dependent on the sudden destruction of organisms with liberation of their endotoxins

THE EXPERIMENTAL PRODUCTION OF SYPHILITIC OPTIC ATROPHY

The only report dealing with this question familiar to me is that of Igersheimer (1918) who says he has seen degenerative processes in the optic nerves of rabbits "several times" He gives the protocols of 4 experiments in all of which the animals were infected by the injection of an emulsion of *T pallida* into the common carotid artery In three of the animals there were extensive lesions in choroid and retina, and the author regarded the accompanying optic atrophy as ascending in character, and due to the injury to ganglion cells In one animal only was there a moderate degree of optic atrophy without marked intraocular changes, here the pathologic picture was quite similar to that seen in tabetic optic atrophy The artificial conditions of these experiments makes them valueless for elucidation of the problem of optic atrophy in man

Spielmeyer (1906) reports that in dogs infected with *Trypanosoma brucei*, optic atrophy developed in several instances, the apparently

primary degeneration extending through the whole visual tract, from the optic nerve to the visual centers In these cases there was no inflammatory change in the vessels It is of extreme interest that in these dogs, there were also degenerative changes in the posterior columns of the cord and in the roots of the fifth cranial nerves, thus producing a close analogy to the lesions of tabes in man

THE TREATMENT OF PRIMARY OPTIC ATROPHY

Only a brief perusal of the older literature suffices to show that the treatment of primary optic atrophy prior to the introduction of salvarsan was almost never of benefit, and that the process progressed inexorably to blindness at approximately the same rate as if nothing had been done With the introduction of modern anti-syphilitic drugs, there began to appear individual case reports, some of which claimed improvement in or arrest of the process, while others spoke of the deleterious effect of the arsenicals in hastening the onset of blindness Also, scattered here and there in communications dealing with the general subject of the treatment of neurosyphilis are allusions to partial successes or failures of treatment I have made no attempt to collect material from all possible sources, preferring to limit this survey largely to papers which consider the treatment of optic atrophy as a special problem and which report a sufficient number of cases to lend weight to their conclusions

Perhaps due to the prominence accorded the use of atoxyl as an anti-syphilitic agent prior to the introduction of salvarsan, and subsequently in the treatment of trypanosomiasis, and to the fact that atoxyl was known to produce optic atrophy, the impression gained among ophthalmologists that arsenical drugs were potentially dangerous to the eye This has been reflected in ophthalmologic literature in statements that the arsenicals should not be used in any form of ocular syphilis and should be especially avoided in optic atrophy The feeling has not been lessened in the minds of ophthalmologists by the fact that no sooner had the agitation over atoxyl died down, than tryparsamide, an atoxyl derivative also having a deleterious effect upon the optic nerves in a certain proportion of cases, was introduced into the therapy of syphilis Although many observers, important among them Igersheimer, have shown that arsphenamine (salvarsan) and

its immediate derivatives have no deleterious effect of any kind upon any of the structures of the eye, and though this has been amply demonstrated in practice by the injection of millions of doses of these drugs, the belief persists, and is hard to eradicate Recent articles by Zimmermann, Chambers, and Stokes have perhaps aided in clarifying this situation

However, a few years experience with the arsphenamines in the treatment of optic atrophy sufficed to show that little more was to be gained from their routine use than by the older methods with mercury Although one occasionally met with an individual success, usually in a patient with a very early atrophic process, it was never possible to be sure that this did not represent a spontaneous remission In the vast majority of instances the speed of progress of the atrophy was not altered, unless for the worse, and blindness ensued as rapidly as if nothing had been done Moreover, a considerable number of cases accumulated in which visual failure was promptly accelerated at the start of a course of treatment Though these were usually patients with an already far advanced and rapidly advancing atrophy, the evident occasional production of a Jarisch Herxheimer reaction in the diseased nerve and the sudden extinguishing of vision in such cases strengthened ophthalmologic opinion that the arsphenamines were contraindicated in optic atrophy

Behr has been an indefatigable writer on the treatment of optic atrophy, and his opinions as to the results obtained from all standard methods of treatment except subdural or fever therapy, may be regarded as representative of ophthalmologic thought He says (1926) that in more than 100 cases treated by him with mercury, bismuth and the arsphenamines, each alone, and in all possible combinations (except subdurally), and with the more modern fever therapy, including malaria, he has never seen a cure There was never improvement in any genuinely progressive case, and all such patients became blind in the orthodox period of time Although he has had no personal experience with the subdural method of treatment, he finds the results of others unconvincing Not only has he failed to observe any beneficial result from treatment, but he has also seen visual failure accelerated by it, and he provides brief reports of 6 such cases treated by routine methods, and one additional case treated with malaria As

a result of these experiences, he thinks all treatment should be withheld from patients with primary optic atrophy, at least until the atrophic process has become complete

John (1929) agrees with Behr He has treated a large number of patients with optic atrophy, of whom he was able to follow only 28 for periods of time ranging from 2 months to 3 years Twelve of these patients were treated with potassium iodide only, of these, six were "favorably influenced" The remaining 16 were treated with various other methods (no accurate details given), and of these only four were favorably influenced Since no data are provided as to the degree of atrophy in the two groups, as to the type or duration of treatment, nor as to the rate of progress after treatment, one can only feel that John, like Behr, is unduly pessimistic in deciding from this experience that treatment is hopeless

It is only fair to say that not only ophthalmologists, but many neurologists and syphilologists, including those of such wide experience as Stokes, for example, are therapeutic nihilists as to primary optic atrophy, having seen little benefit from treatment

Behr points out with much justice that it is extremely difficult to evaluate the results of treatment in an individual case, since the rate of progress of the atrophic process is so variable (a few months to many years before blindness ensues), and since spontaneous remissions occur so often As to the variability of progress, our personal experience is in thorough accord, spontaneous remission has, however, seemed to us to be a comparatively rare phenomenon Behr also emphasizes the facts that to speak with any authority concerning treatment results, the investigator must have observed a large number of cases over a long period of time, so as to be sure that a favorable outcome occurs more frequently and lasts longer than in control untreated groups, and that many of the published reports so far have lacked essential ophthalmologic details He insists that before, during, and after treatment the eyes must be under the careful observation of a competent ophthalmologist The present study of the literature, though it leads to conclusions as to the efficacy of treatment diametrically opposite to those of Behr, support these contentions The reasons for the prevailing feeling of hopelessness among ophthalmologists lie in the facts that it is difficult for any single observer to amass a

sufficiently large series of treated patients followed for a long enough time, that reports appear as a part of the discussion of the general problem of treatment of neurosyphilis and are thus submerged in relative obscurity, and that few of them provide sufficient ophthalmologic details to be convincing to the reader In dealing with a disease process the outcome of which has heretofore been uniformly unfavorable, it does not suffice for the investigator to report that he has treated so many cases with improvement or arrest He must define his material sufficiently carefully so that the reader may be aware of the degree of atrophy and the approximate rate of its progress before treatment, he must not only describe his treatment method but provide details as to how much was given and over how long a period of time, and he must above all have followed his cases for years, not for weeks or months Further reading of this paper will show to what extent the available published reports are deficient in these respects However, it is unwise entirely to condemn a method of treatment as Behr condemns subdural therapy, because its users have failed to provide accurate ophthalmologic studies Statements as to visual acuity are often available, and after all, the success or failure of a given method of treatment in any series of cases can readily be measured by ability to see versus blindness If useful vision can be maintained for a period of years, it matters little to the patient whether there have been detailed records of visual fields, etc , throughout his illness

In evaluating treatment results in optic atrophy, a certain amount of common sense is essential It is quite obvious, from what has been said of the pathologic anatomy of the condition, that when a patient is completely blind and the fibres of the optic nerve completely degenerated, vision cannot be restored Dead nerve fibres cannot be replaced by living ones If our own experience is typical of that of others, it is a distressing fact that the majority of our own patients are blind or nearly so when first seen If any form of treatment is to be successful, it must aim, not at the replacement of dead nerve fibres, but at the arrest of the degenerative process The ultimate success or failure of treatment therefore depends entirely on whether it can be started while enough living nerve fibres remain so that, if they can be preserved useful vision is retained It is difficult if not impossible to

set up a criterion of this applicable to every case Certainly it cannot depend on the degree of pallor of the discs, since we have already seen that the discs may be chalky white in the presence of normal central vision, nor can it depend on the visual fields, for they may be concentrically contracted to a marked degree while central vision is normal or only slightly reduced The standard which we adopted some years ago as a rough working basis (Moore 1927) is that if central visual acuity in the better eye is 20/60 or more, there is some hope of retaining useful vision, while if vision in the better eye is less than this, the prognosis is bad

It is also important to determine whether there are other factors than the degree of visual acuity before treatment, which may aid in estimating the probable success or failure of a treatment method The rate of progression of visual failure is certainly an important consideration to which little attention has been paid in the literature It is unlikely that as good results can be obtained from any method of treatment in a rapidly progressive atrophy as in a patient with only slow visual loss Many ophthalmologists have laid stress on the type of alteration in the visual fields as being an exact indication of the location and extent of the pathologic change in the optic nerves and as an indication for giving or withholding treatment Wilbrand and Saenger (1913) differentiate two types of optic atrophy, one with gradual diminution of central vision and progressive contraction of white and color fields, the other with concentric constriction of form fields with normal central vision and maintenance of color vision in the functioning portion of the visual field In the first of these, they believe the involvement of the optic nerve to be diffuse, and treatment to be contraindicated In the second, the lesion involves peripherally placed fibres principally, and treatment is strongly advised Behr (1916) describes three types of field changes in which he believes treatment to be contraindicated These are (1) decrease in central vision and early loss of color vision with normal or nearly normal fields for form, (2) marked constriction of white and color fields with normal or nearly normal central vision, (3) slight changes only in form rather than color fields, normal or nearly normal central vision, but the ophthalmoscopic picture of advanced atrophy

Arlt (1922), in describing the results of treatment with the arsphen-

amines, mercury, and potassium iodide, divides his 53 cases into three groups Eighty-five per cent of his patients showed simultaneous bilateral loss of visual acuity, and constriction of form and color fields This he interprets to mean diffuse involvement of the whole optic nerve Here the prognosis was uniformly bad, treated or untreated, these patients progressed to complete blindness in an average period of about two years A second group, comprising about 9 per cent of his patients, showed sector defects in the visual fields, instead of concentric constriction (no details as to visual acuity) In this group, the prognosis was relatively good He separates into a third group those with central scotomas, who made up 6 per cent of his material Here also the prognosis was fair for preservation of useful vision Arlt brings out the point, more strongly stressed by Lederer (1928), that the outlook is much worse when vision fails in both eyes simultaneously than when treatment can be started while the atrophic process is still apparently unilateral, and visual acuity and fields in the better eye are still normal or nearly so Unfortunately, Arlt gives no detailed information as to the type of treatment used, the number of cases treated or untreated, nor the results observed in the two groups He did not employ subdural or fever therapy

SUBDURAL (INTRASPINAL OR INTRACISTERNAL) TREATMENT

Prior to the introduction of the subdural method of treatment by Swift and Ellis (1913), the prognosis of optic atrophy was, as has been pointed out, completely or almost completely hopeless Since 1915, however, there have been accumulating here and there reports which lend a different aspect to the situation Swift and Ellis themselves reported arrest of the process in a few cases, using their technique of intraspinal arsphenaminized serum Gennerich (1916, 1922), in Germany, also advocated intraspinal treatment with neoarsphenamine dissolved in the spinal fluid of the patient and reported several successful results

In 1916, Schoenberg, in a long and carefully considered paper dealing with the anatomy and physiology of the central nervous system, carried out intravital staining experiments with trypan blue and lamp black He found that these substances could not be brought into contact with the optic nerves or their sheaths when given by the in-

travenous route, but only when given by intraventricular (and cisternal?) injections He considered the applicability of this fact to the treatment of optic atrophy, although he did not then report having used such a method of treatment himself He accepted the idea that optic atrophy was due to the presence of *T pallida* in the optic nerves, and felt that the only hope of relieving it was to introduce medicated substances subdurally The ideas of Schoenberg (and many others preceding and following him) as to the relative impermeability of the nervous system and cerebrospinal fluid to drugs introduced intravenously have been abundantly confirmed Schoenberg subsequently reported (1920) on the results of the intraspinal or intraventricular

TABLE 3

Schacherl's results with intraspinal treatment in optic atrophy

CASE NUMBER	VISION BEFORE TREATMENT		VISION AFTER TREATMENT		PERIOD OF OBSERVATION	THERAPEUTIC RESULT
	O D	O S	O D	O S		
1	6/12	6/18	6/18	6/24	5 months	Slow failure
2	L P	6/18	Hand movements	6/24	4⅓ years	Arrest
3	6/6	Blind	6/5	L P	2⅔ years	Arrest
4	Cannot be determined from available data		6/38	6/8	10 months	Arrest
5	F 1 5 meters	F 2 5 meters	3/60	3/60	4⅙ years	Improved

In this and subsequent tables, L P = light perception, F = fingers

treatment of 8 patients with optic atrophy In 3 the process was apparently arrested, five became worse in spite of treatment Judged by present day standards, the amount of treatment given was inadequately small in all instances

In 1923 Schacherl reported on the subdural treatment of primary optic atrophy in a series of 64 patients, of whom only 5 had been under observation for a long enough period of time to make him fairly certain of the permanency of his results His treatment scheme was one of combined intravenous and intraspinal injections, the latter of 0 25 to 1 mgm of neoarsphenamine dissolved in spinal fluid or salt solution Such injections were continued (intervals not stated) until the spinal

fluid serology had become negative and for several doses thereafter His results were as shown in table 3 Of the remaining 59 patients in his series, 31 had been lost track of, 2 were completely blind when treatment was started, 22 were still under treatment, and in 4 treatment had recently been completed with good results though the observation period was too short to include them in the report In a subsequent publication (1927), Schacherl confirms his earlier opinion, and states that his series now includes 31 cases "benefited" by intraspinal treatment He gives no further details, and does not mention the number of unsuccessful treatment attempts He states that there is no danger of aggravating the visual failure by this method of therapy, as a number of observers have suggested that there is with malaria, and he regards intraspinal treatment as the only method which holds out any hope for the patient with optic atrophy

In 1924 Fordyce reports,

"in optic atrophy the result of a basilar meningitis, the use of methods of treatment demonstrated to be futile or of little value is wasted effort and results in the loss of valuable time Persistent intraspinal treatment when indicated by the fluid findings can arrest its progress and often preserve a useful amount of vision Our statistics show 33 cases which were under observation and treatment, of whom 9 were of the simple optic atrophy type, 17 of the tabetic type, and 7 of the paretic type Eight had almost complete atrophy of both eyes before treatment was undertaken No amelioration was brought about Seven had complete atrophy of one eye and partial in the other Two of these progressed and 5 became stationary Seventeen had incomplete atrophy of both eyes In 12 improvement took place and the process was arrested In 5 a further reduction of the visual field was noted before arrest of the process The majority of these patients were controlled by well-known eye men, and the fields of vision taken before, during, and after treatment In 5 of the patients arrest of the atrophy has been confirmed from two to five years after negative blood and fluid"

Stokes and Shaffer, on the contrary, reported in 1925 that, "In ten cases of the primary type (of optic atrophy) we were unable to record a single improvement Occasionally, in the very earliest cases it seems possible to arrest the process" Unfortunately, it is impossible to tell to what extent, if at all, intraspinal treatment was

used in these cases, though in a subsequent paper, Stokes says, "I have not seen intraspinal therapy produce results notably superior to those obtained by mercury and intravenous iodide"

Zimmermann in 1925 reported a careful study of 7 patients treated intraspinally He draws a distinction between tabetic optic atrophy and that due to basilar meningitis, believing that the prognosis is better in the latter type As already pointed out, however, it is probable that the process is essentially the same in either case, and

TABLE 4

Zimmermann's results in tabetic primary optic atrophy

CASE NUMBER	VISION BEFORE TREATMENT		TREATMENT	VISION AFTER TREATMENT		PERIOD OF OBSERVATION	ZIMMERMANN'S SUMMARY
	O D	O S		O D	O S		
1	20/70	15/100	12 I S	20/30	Not given	3 years	Arrest
2	20/200	20/20	4 I S	10/200	20/20	2 years	Slow progress
3	20/25	20/30	12 I V. 5 I S	20/20	20/20–3	Short duration?	Improved
4	20/30	20/50+	6 I S	20/60	20/60	2 years	Slow progress
5	20/40	20/70	16 I V 4 I S	20/200	20/100	5 years	Slow progress
6	20/25	20/25	6 I S	Blind	20/70	10 months	Worse
7	20/40	20/40	4 I S	H M	H M	2 months	Worse—due to treatment

that differential diagnosis is always difficult and often impossible His results may be summed up as in table 4 (all patients with tabetic primary atrophy) It is worth noting that all of these patients were inadequately treated by present day standards Data as to visual fields are provided in all· in general the fields were maintained at their original level, or nearly so, when vision was preserved

Moore (1927) reported the results of intraspinal treatment in 20 patients with primary optic atrophy, in all but one of whom visual acuity in the better eye was as good as 20/60 He felt that if visual

acuity in the better eye was less than 20/200 when treatment was begun, little could be hoped for from any form of therapy In fourteen of twenty patients, visual failure was arrested In five, visual acuity and fields were improved over the admission examination, and in nine, the process remained stationary In a much larger series of cases treated with arsphenamine intravenously without intraspinal treatment or with mercury, bismuth and potassium iodide, every case progressed inexorably to blindness These cases were reported as a part of a larger study of the results of treatment of central nervous system syphilis and details as to visual acuity, visual fields, amount of treatment given and the period of subsequent observation were not

TABLE 5

The results of intraspinal treatment in optic atrophy (Moore)

CLINICAL RESULT	SEROLOGIC RESULT				
	Excellent	Good	Fair	Poor	Total
Improved	3			2	5
Stationary	4	1	2	2	9
Worse	1			5	6
Total	8	1	2	9	20

In 70 per cent a satisfactory clinical result was obtained
In 40 per cent an excellent or good serologic result was obtained
In 40 per cent an excellent or good combined result was obtained

provided A subsequent report of these and additional cases will supplement the present paper

Gifford and Keegan (1927) have been utilizing the same principle of treatment, applied in a different way They have employed intracisternal injections of 0 5 mgm of bichloride of mercury (0 1 cc of a 1/200 solution diluted with 15 to 20 cc of the patient's spinal fluid) Certainly the cisternal route would appear to be preferable to the intraspinal, since it has been repeatedly shown that substances introduced into the cisterna magna reach the base of the brain sooner and in higher concentration than when they are introduced into the lumbar sac This is probably true even when their diffusion from the lumbar area is aided by posture (elevating the foot of the bed) Gifford and Keegan report 14 cases of optic atrophy treated by this method In

one there was marked improvement, maintained for 5 years In 5, the better eye remained unchanged and the authors consider the process to be arrested Four patients were slightly worse and two much worse, but none were blind The observation period ranged from 9 months to 5 years One would like to know ophthalmologic details which are lacking

Viner and McMurtry (1925) also report two cases treated by Gifford and Keegan's method In one there was slight but definite improvement and in the other, the atrophic process appeared to have been arrested

Meesman and Roggenbau (1929) treated 21 cases of optic atrophy (no details as to degree of visual failure before treatment) with a system including the intraspinal injection of 0 001 gm neosalvarsan dissolved in spinal fluid, together with intravenous neosalvarsan and intramuscular bismuth injections In two patients, the process was arrested, in one, vision failed rapidly during treatment The remaining 18 all grew slowly worse, but the rate of progression of the atrophy appeared to be definitely slowed up These patients were observed for periods of time ranging from 2 to 30 months

Jaensch (1930) reports the results of subdural treatment with arsphenaminized serum (Swift-Ellis technique) combined with intravenous neoarsphenamine and intramuscular bismuth, in 18 patients It is not possible to tell how much treatment he gave to any patient He divides his patients into three groups group 1, vision in the better eye more than 1/10, 7 patients, all blind in 2 to 27 months No details are given as to how much better than 1/10 was visual acuity in any case Group 2 included 7 patients in whom vision in the better eye was 1/10 to finger movements at 2 metres, of these 4 are stationary, or only slightly worse, and 3 are blind, in periods of time ranging from 4 to 24 months Four patients were in group 3, in whom vision was less than finger movements at 2 metres, and two of these are slightly improved On the basis of these results the author is pessimistic as to the outcome of treatment

The same patients are discussed from the general standpoint in a separate communication by Rotter (1930), who omits all ophthalmologic details Only 10 of the 18 were re-examined from the neurologic standpoint Of these 5 are reported as stationary or improved, 4

slightly worse, and only 1 progressive Presumably these results are an expression of the general neurologic, rather than the purely ophthalmologic, status Rotter also reports in the same manner on the malaria treatment of 6 tabetics with optic atrophy His findings are shown in table 6 The clinical and serologic outcome are only roughly parallel Rotter is a strong advocate of the value of intraspinal or intracisternal treatment by the Swift-Ellis method in tabes, and especially in beginning optic atrophy, and draws from the same series of patients more encouraging conclusions than does his ophthal-

TABLE 6

Rotter's results in tabes with optic atrophy, expressed from the neurologist's standpoint

	NEUROLOGIC RESULTS	SEROLOGIC RESULTS
Subdural treatment		
Markedly improved	1	2
Slightly improved	2	14
Stationary	2	
Slightly worse	4	
Progressive	1	
Malaria		
Markedly improved		1
Slightly improved	2	4
Stationary	3	
Progressive	1	

* Only 10 of the cases treated were re examined

mologic confrere Jaensch This is partly due, of course, to Rotter's more generally neurologic point of view

Vranešić (1930) provides an interesting discussion of intraspinal versus intracisternal treatment He takes the viewpoint that the cerebrospinal fluid represents a stagnant fluid system, and that foreign substances introduced into it diffuse upward or downward from the point of introduction by virtue of their specific gravity as compared with that of spinal fluid, and of the position of the patient In rabbits, human cadavers, and living paretic patients, he has shown that if blood serum or a 10 per cent solution of sodium iodide is injected subdurally into the lumbar sac, the patient being kept sitting upright

or in a horizontal reclining position, diffusion of serum proteins or of iodine into the cisternal or ventricular fluid takes place only very slowly and in small amounts If, on the other hand, the injection is intraventricular or intracisternal, these substances appear promptly in the lumbar spinal fluid, and within a very few minutes are equal in concentration to that in ventricular or cisternal fluid The explanation of this lies, of course, in the high specific gravity of blood serum (1027–1030) or 10 per cent sodium iodide (1082) as compared with that of spinal fluid (0 99–1 000) Utilizing this principle in treatment, Vranešić has further shown that when blood serum is injected intraspinally in the lumbar region, serum proteins can be made to appear promptly and in high concentration in cisternal or ventricular fluid provided the patient is placed in an appropriate position Immediately after treatment, the patient is laid face down across a bed, his hips at the extreme edge of the bed, his weight being supported by his thighs and legs on the bed, and by his crossed forearms on the floor, his head cushioned by his arms He is left in this position, almost literally standing on his head, for 15 to 25 minutes, then he is put to bed without a pillow, with the foot of the bed elevated about a foot, for 10 to 15 hours Under these circumstances, it is interesting to note that the concentration of serum protein in the cisternal fluid rises from 0 3 per cent (Brandberg's method) to 3 7 per cent at the end of about 30 minutes and is maintained at this level for at least two and one-half hours

Vranešić has treated 16 patients with optic atrophy by this modification of the Swift-Ellis technique Of these, 10 were improved, i e , in several, visual acuity before treatment improved by about one-third, others improved from 1/10 of normal vision before treatment to 3/4 afterward Four patients remained stationary, and two others, both able only to count fingers before treatment, were uninfluenced and gradually became worse No details were provided as to the amount of treatment given nor as to the length of observation Vranešić is enthusiastic over the results obtained

The whole question of the value of subdural therapy in neurosyphilis, whether intraspinal, intracisternal, or intraventricular, has been the subject of much debate, some of it acrimonious The original unbounded enthusiasm was met by an equal complete scepticism of

its worth These opposing viewpoints led to a critical examination of the method by which this form of treatment affected its improvement, if any, and three main theories were elaborated That the insignificant amount of drug introduced could be of any real treponemicidal importance seemed improbable, even if its treponemicidal activity were enhanced or supplemented by its presence in serum (Swift and Ellis) The subdural introduction of medicated serum, or of an irritating arsenical or mercurial drug, is known to set up a sterile meningitis, and it has been thought that this meningitis itself might be of therapeutic value, either from the hyperemia which it induces, or because its occurrence alters the permeability of the blood-spinal fluid barrier, so as to permit the entrance into the spinal fluid and nervous system of drugs introduced intravenously, and which otherwise would not reach the desired point in sufficient concentration to be of value

The passage of time has also done much to clarify the usefulness of subdural therapy in various types of neurosyphilis It is now more or less generally agreed that it is of value in certain selected cases, chiefly of tabes dorsalis, though there is as yet no agreement as to which of the three factors mentioned above brings about the improvement Although in the present connection this point would seem to be of academic importance only, the question as to the mechanism involved has perhaps been reopened by the work of Horn and Kogerer (1929), and of Fazakas (1929) These observers, feeling that aseptic meningitis, whether because of hyperemia or because of disturbance of the blood-spinal fluid barrier, was the important feature of subdural treatment, undertook to produce a sterile meningitis by intraspinal or intracisternal air injections Fazakas has treated 9 patients with optic atrophy by this method and Horn and Kogerer three Inasmuch as the latter workers omit to supply such important details as visual acuity before treatment, and as they also used malaria almost simultaneously, their results are too unreliable to be quoted Of Fazakas' 9 cases, adequate details are available in only 5 His method of treatment is to give an intracisternal air injection every 10 days, in the midst of a series of bi-weekly injections of neoarsphenamine (to a total of 5 to 7 gm) or silver arsphenamine (to a total of 3 to 5 gm) Recently he has been giving 0 5 to 3 mgm of salvarsan intracisternally All five of his patients had relatively early optic atrophy

As a result of treatment, four were slightly improved and one was stationary after observation periods ranging from one to six years

In table 7 an attempt has been made to summarize the results obtained from various modifications of the subdural method of treatment The experience of certain investigators, such as Stokes, has been eliminated because of the absence of details When sufficient details were available, I have also eliminated from consideration all patients who were blind before treatment was started, and a few more in whom various data were too inadequate to permit inclusion The information provided does not permit any further analysis on the basis of

TABLE 7

Summary of results obtained from subdural treatment

AUTHOR	TOTAL CASES	IMPROVED	STATIONARY	WORSE
Schacherl	5	1	3	1
Fordyce	24	12	5	7
Zimmermann	7	1	1	5
Moore	20	5	9	6
Gifford and Keegan	12	1	5	6
Viner and McMurtry	2	1	1	
Fazakas	5	4	1	
Jaensch	18	2	4	12
Schoenberg	8		3	5
Vranešić	16	10	4	2
Meesman and Roggenbau	21		2	19
Total	138	27	48	63
Per cent		54		46

visual acuity before treatment, visual field changes, or rate of visual failure Generally speaking, classification as "improved" means little more than the less striking word "stationary," since in practically all patients the improvement, if any, was very slight, and consisted only in a slight increase in central visual acuity, or a slight widening of concentrically constricted form fields, or both In 54 per cent of the 138 patients treated, a favorable outcome resulted, amounting essentially to the arrest of rapidly progressive visual failure, the progress being stopped over periods of time ranging from a few months to 5 to 6 years It cannot be determined whether this arrest or improve-

ment left the patient with useful vision, obviously this was often not the case, since when treatment was started, the atrophic process was far advanced in many instances Of the 63 patients classified as worse, some are blind, and in a few the onset of blindness was precipitated by treatment, but since blindness is certain if treatment is withheld, this cannot be urged as an objection to the treatment method In general the rate of progress after treatment seemed slower than before

Taking into consideration the fact that these figures include patients with all degrees of optic atrophy (excepting those already completely blind), these figures appear to provide incontrovertible evidence that something can be accomplished by the treatment of primary optic atrophy, and that in subdural therapy of one or another sort, a method is at hand which is well worth further study and much more extensive application The data do not provide evidence as to the best method of treatment, whether intraspinal or intracisternal, whether arsphenaminized serum, neoarsphenamine or mercury dissolved in spinal fluid, air injections etc , nor can anything be said as yet as to the permanency of the results achieved, nor as to the type of patient most likely to be benefitted or harmed by treatment It seems obvious, from *a priori* reasoning, that the earlier treatment can be started, the better the prospects of success, and that intracisternal treatment is likely to prove more effective than intraspinal since its effect, of whatever nature, is produced in much greater intensity and in closer proximity to the diseased area It is also apparent that one or a few treatments are not sufficient, on the contrary, it is probably desirable to continue at least until the serology of the spinal fluid is negative and perhaps for a few treatments thereafter It must not be forgotten, as Rotter has emphasized, that the patient with optic atrophy has also other lesions of neurosyphilis, even though they may not be detectable clinically, and that he may have lesions of syphilis in important viscera outside the nervous system Treatment for the average neurosyphilitic is measured in terms of years, not of a few months

Much further study is needed and it is hoped that a survey of our own material, to appear subsequently, will be of service in answering some of the more obscure points as to treatment In the meanwhile, enough has been said to show that subdural treatment of some type

is of sufficient value to deserve much more widespread and patient trial, that nothing is gained by preliminary treatment with intravenous arsphenamine products, mercury, bismuth or the iodides, and that, indeed valuable time may be lost by failure to adopt subdural treatment immediately.

THE USE OF TRYPARSAMIDE IN OPTIC ATROPHY

Tryparsamide (n-phenyl glycine amide of p-arsonic acid) is a pentavalent arsenical drug which is of great value in the treatment of central nervous system syphilis Like atoxyl, it has a tendency to produce visual damage in the normal eye, probably from elective localization in the optic nerve About 10 per cent of all patients treated with it develop blurring or dimness of vision, and of these about half show objective evidence of visual damage in the form of concentric constriction of the visual fields and diminution of central visual acuity without scotomas These changes precede any ophthalmoscopic evidence of atrophic changes in the nerve and if the administration of the drug is promptly stopped at their appearance, may spontaneously disappear in a few weeks or may persist for an indefinite time In a few instances and even though the drug has been discontinued, there may be a very slow progression of field constriction and increasing pallor of the nerve, leading to confusion in diagnosis with a genuine primary atrophy due to syphilis The only differential diagnostic points are that (1) visual acuity, fields, and fundi were known to be normal before treatment with tryparsamide, (2) the subjective complaint of blurred vision with accompanying constriction of the peripheral fields was known to occur suddenly and in direct relation to treatment with the drug, (3) the progress of the atrophy is very much slower than that of atrophy due to syphilis, and (4) central visual acuity usually returns promptly to its original level within a few weeks of the appearance of the reaction and remains normal in spite of slow progression of field constriction

Woods and Moore (1924) observed untoward visual reactions from the use of tryparsamide in 21 per cent of patients with neurosyphilis and in only 6 per cent of patients in whom central nervous system disease could be excluded Among neurosyphilitics, reactions occurred in 23 per cent of the tabetics and paretics treated (the type

of neurosyphilis in which optic atrophy is most likely to occur), and in only 15 per cent of patients with other forms of neurosyphilis These figures indicate that tryparsamide is more likely to produce visual damage in patients in whom the optic nerves are already actually (or potentially) diseased than in normal individuals When the use of the drug was first begun, we felt (Moore, Robinson and Keidel, 1924) that any patient with pre-existing disease of the optic nerve or retina and especially with optic atrophy, should be rigidly excluded from tryparsamide treatment Subsequent experience (Woods and Moore) showed that this was too sweeping a statement Twelve patients with optic atrophy were treated with tryparsamide, and in only four was there any evidence of visual damage from its use One of these four patients, an individual with slowly progressive optic atrophy of moderate degree, was precipitated into sudden blindness after the second dose of the drug On the other hand, however, Woods and Moore saw nothing to indicate that tryparsamide was of marked value in optic atrophy Though their patients were studied rather from the standpoint of the possible deleterious effect of tryparsamide than from that of the treatment of optic atrophy, they saw no improvement in any patient, and the progress of the atrophy did not seem to be arrested Since that report, further experience has led us to take the position that, since other methods of treatment (subdural or fever therapy) are more likely to be productive of good results, and since tryparsamide is potentially dangerous even to the normal eye, its use in optic atrophy should be avoided unless other features of the individual case (the association of general paresis, for example) seem to render its use imperative, or unless the atrophy is already complete and the patient blind If the drug must be used in a patient who still retains some vision it should be done only under the most painstaking ophthalmologic control

Cady and Alvis (1926) administered tryparsamide to 16 patients with optic atrophy Of these, three became blind, and in one instance this was apparently due to the drug, three others became definitely worse In two cases, there seemed to be definite improvement, and in 8, the degree of visual impairment remained unchanged No details are given as to ophthalmologic findings, or as to the length of observation Although these results seem not dissimilar from those

of Woods and Moore, Cady and Alvis arrive at opposite conclusions While they recognize that patients with optic atrophy are more liable to injury by tryparsamide than those with normal eyes, they feel that the generally unfavorable results of other forms of treatment justify its use

FEVER THERAPY IN OPTIC ATROPHY

The successful introduction of the malaria treatment of paresis by Wagner-Jauregg and his associates (1917) brought about, as with all new forms of treatment, its application to all other types of neurosyphilitic involvement Many other methods of artificially producing fever have also been tried, as for example, relapsing fever, rat-bite fever, foreign protein injections, hot baths and diathermy The favorable results of malaria treatment in paresis are well known, the results obtainable from the other methods mentioned are also good, but in general not quite as good as with malaria In other types of neurosyphilis, however, and especially in tabes, the results of fever therapy have not been so striking as in paresis

In optic atrophy, fever therapy has also been tried, and reports are now beginning to accumulate, especially from Germany As mentioned above, Behr treated 6 patients with malaria Five of these were already blind before treatment, in the sixth vision decreased within two or three days after the onset of malarial paroxysms from 6/7 to 3/60 On the basis of these six cases Behr, with his usual pessimism, condemns the use of malaria and falls back on what one can hardly fail to regard as his *idée fixe*, that all forms of treatment should be withheld

Elschnig (1925) reports the results of malaria treatment in 18 patients with optic atrophy In five, visual acuity before treatment ranged between 6/36 and 6/8 in the better eye, one of these patients became worse during the malaria, and in four, the process was arrested for 3, 3, 4, and 13 months, respectively Six patients had vision ranging from finger movements to 3/36 in the better eye before treatment, all of these progressed In 7, vision before treatment was limited to light perception, three of these became completely blind, and in 4 there was no change during a short observation period Elschnig concludes that malaria therapy is advisable only in patients with early optic atrophy

Fisher-Ascher (1926) reports on the status of these same patients (from Elschnig's clinic) at a slightly later date There was no material change in the result in any patient

Bering (1926) treated 6 patients with malaria One early case was stationary about 2 years after treatment Two others, more advanced, were also stationary about 18 months later Three were worse, but in two of these the rate of downhill progress before treatment had been very rapid, while after treatment it was markedly slowed

Wagner-Jauregg (1927) has treated a number of patients (exact number not given) and states that a small number improved slightly, and that in a larger proportion, the process was apparently arrested over a period of 2–3 years, though downhill progress before treatment was more or less rapid In a still larger number of cases, the atrophy progressed after treatment, but Wagner-Jauregg thinks that the rate of its progress was considerably slower than before He agrees with Behr that all other forms of treatment of optic atrophy (except fever therapy) are hopeless, but believes that the results obtained from malaria are sufficiently encouraging to warrant further extended trial

Two cases are briefly mentioned by Fleischer (1927) One, treated with malaria, was apparently arrested two years later, the same favorable result, over a period of several months only, was produced in the second by relapsing fever

Schacherl (1927) has also treated a number of cases with malaria and, although he provides no details, is unfavorable to the method because in some cases, rapid visual failure occurred during the course of the fever He has seen such cases in which, after interruption of the malaria, visual acuity did not return to the pre-treatment level, or if so, only very slowly

Sabbadini and Pisani (1928) treated 8 patients with malaria The degree of atrophic change ranged from slight to severe Within one to four weeks after completion of the malaria, reexamination showed definite improvement in four cases (especially in the visual fields), slight improvement in three, and one patient with an associated chorioretinitis was worse They feel that in view of the hopelessness of other methods of treatment, malaria therapy should be tried in all

cases, especially early ones They recognize that the observation period in their cases was too short to permit definite conclusions

Winkler (1928), in treating three patients with malaria, had an experience similar to the discouraging one of Behr, in that in one case, vision fell off so rapidly and alarmingly after the fourth paroxysm that the malaria had to be terminated This experience, and the conflicting reports in the literature, lead Winkler to feel that another method of producing less intense fever, used in combination with anti-syphilitic drugs, might be worth trying He therefore devised a method of administering 0 2 to 0 3 cc of a 0 5 per cent suspension of sulphur in olive oil, at the same time giving an injection of bismuth This procedure causes a rise in temperature to 100 to 101°F He treated 5 patients with optic atrophy with this method (no further details given) and of these, 3 were stationary or slightly improved in 5, 8 and 18 months respectively

This paper is mildly interesting in connection with a communication from Horn and Kauders (1928) These authors think that the cause of the sudden visual failure in patients with optic atrophy treated with malaria may be the very high temperatures Inasmuch as they are of the school which holds that there is some other factor in malaria therapy than temperature responsible for the favorable effect in neurosyphilis, they feel that there might be less danger and more promise of a successful outcome in optic atrophy if malaria could be induced and carried through 8 to 12 paroxysms without such high temperature peaks Accordingly they found that by giving 0 005 gm quinine, on the two days following inoculation and the same dose daily after the paroxysms had begun, the temperature peaks could be held to 102°F or less without interrupting the course of the malaria The quinine is given during the period of defervescence They treated 5 patients with optic atrophy by this method There were no bad results and in 2 cases there was slight improvement The post-treatment observation period was, however, very short

Later reports than these are less encouraging Havel (1929) treated 16 patients He gives no details except that 9 became worse during or shortly after treatment, and in 7 there was no change after a short observation period Wolff (1929) also treated 16 patients, and was unimpressed by the results obtained Meesman and Roggenbau

(1929) observed a number of instances of optic atrophy in paretics treated with malaria The results, so far as the optic atrophy was concerned, were uniformly bad In two patients, vision failed rapidly during, and apparently as a result of, malaria O'Leary and Brunsting (1930) have treated 15 patients, and saw no beneficial effects [2] In all the progress of the atrophy was progressively downhill In the 6 cases reported by Jaensch (1930), the results were uniformly bad

Hessberg (1930) reports on 11 patients treated with malaria His results are capable of summarizing in tabular form One patient

TABLE 8

Hessberg's results with the malaria treatment of optic atrophy

CASE NUMBER	VISION BEFORE TREATMENT		VISION AFTER TREATMENT		PERIOD OF OBSERVATION	SUMMARY
	R	L	R.	L.		
1	H M	5/5	H M	5/5	3 years	Stationary
2	5/4	5/4	2/35	5/20	5½ years	Worse
3	5/4	5/4	3/50	5/25	2½ years	Worse
4	5/10	5/25	5/5	5/20	1 year	Better
5	4/50	5/50	1/25	4/36	4 months	Worse
6	H M	H M	Sl impr	Sl impr	1 month	
7	8/50	H M	H M	H M	6 months	Worse
8	5/5	5/5	4/10	4/7	1½ years	Worse
9	5/5	1/100	5/5	No data	1½ years	Stationary
10	L P	5/35	L P	L P	4 years	Worse
11	5/8	5/12	5/15	5/20	4 years	Sl worse

was improved, two were stationary and 8 were worse, but the speed of progress of the atrophy seemed to be slowed up

One or two investigators, among them Wurz (1927), Lederer (1928), and Hessberg (1930), have attempted the treatment of optic atrophy

[2] In a personal communication (November 25, 1931) O'Leary is less pessimistic, as follows Since we started the use of malaria in 1924, we have treated 26 patients with tabes dorsalis complicated by optic atrophy In none of these cases was the vision improved although in 9 there has been no appreciable decrease in vision since the fever treatment. In 8 what vision the patients had at the time of treatment has disappeared and they are practically blind at this time I have insufficient data on the rest but none of the group showed any improvement whatsoever One striking feature is the fact that all of the patients in whom there has been an apparent arrest of the optic atrophy were in the early stages of optic atrophy when the malaria treatment was given "

with fever producing injections of foreign protein with or without the administration of anti-syphilitic drugs Wurz reports 7 cases treated with typhoid vaccine intravenously He saw no deleterious effects from treatment One patient was blind before treatment, four could see only finger movements, and two had as much as 6/50 vision in the better eye Obviously, all had far advanced atrophy Of the 6 with some vision before treatment, one was slightly improved, four were unchanged, and one worse after treatment The period of observation is not stated

Lederer reports the results of phlogetan treatment in five patients, summarized in table 9 Phlogetan is a proprietary German remedy,

TABLE 9

Lederer's results in optic atrophy from non-specific fever therapy

CASE NUMBER	VISION BEFORE TREATMENT		TREATMENT	VISION AFTER TREATMENT		DURATION OF OBSERVATION	AUTHOR'S SUMMARY
	O D	O S		O D	O S		
1	Blind	0 7	Sodium nucleinate, arsphenamine, phlogetan	L P	0 7	4 years	Slight improvement
2	L P	0 9	Phlogetan Neosalvarsan	Blind	1 0	3 years	Arrest
3	H M	0 7	Phlogetan Neosalvarsan	Blind	0 9	5 years	Arrest
4	Blind	0 6	Phlogetan	Blind	0 5	9 months	Slightly worse
5	0 2	0 3	Phlogetan Malaria	F M	F M	3½ years	Worse

protein in nature The author emphasizes the fact that in his cases 1, 2, and 3, the optic atrophy was to all intents and purposes unilateral, vision in the better eye being normal or nearly so before treatment He points out that in these three cases, the good result obtained has persisted 3, 4 and 5 years respectively He feels that since unilateral optic atrophy, the better eye remaining uninvolved, is so extremely rare in an untreated material (Uhthoff saw only 2 such instances among 300 patients), the preservation of vision in the better eye in his three patients can only be interpreted as a result of treatment This being so, such patients offer the most favorable prognosis

Hessberg (1930) has used non-specific fever therapy (with pyrifer,

another German proprietory product) in patients whose general physical condition precludes malaria He reports 5 cases, one of whom, with normal central visual acuity before treatment, has remained stationary for 5 years Two others, with vision in the better eye 5/5 and 5/35, respectively, were unchanged one month after treatment Two others with vision in the better eye 5/15 and hand movements respectively, became blind during treatment

The results of various observers with malaria in optic atrophy are summarized in table 10, patients blind before treatment being eliminated As in the case of subdural therapy, the work of several investi-

TABLE 10

Summary of results obtained from fever therapy

AUTHOR	TOTAL CASES	IMPROVED	STATIONARY	WORSE
Behr	1			1
Bering	6		3	3
Winkler	1			1
Horn and Krauders	5	2	3	
Hessberg	11	1	2	8
Jaensch	6			6
Sabbadini and Pisani	8	7		1
Elschnig	18		8	10
Fleischer	2		2	
Havel	16		7	9
O'Leary and Brunsting	15			15
Total	89	10	25	54
Per cent		39		61

gators is omitted from the table because of incomplete data Of the 89 cases included, a favorable outcome was obtained in 35, or 39 per cent, while 61 per cent progressed in spite of treatment These results are not as good as those obtained from subdural treatment (54 per cent favorable outcome), and in addition, two factors important to a comparison of the two methods of treatment cannot be presented in tabular form In general, the patients who have done well after malaria have been observed for a much shorter subsequent period of time than the similar group after subdural treatment In addition, there is general agreement that malaria is much more likely

to precipitate sudden visual failure during its course than is the subdural method of treatment

General considerations affecting the choice of a treatment method in optic atrophy The results just described from subdural or from fever therapy are an adequate answer to the question as to whether patients with optic atrophy should be treated, or permitted to progress to blindness untreated Obviously, when the progress of visual failure can be arrested in 40 to 55 per cent of the cases, the responsibility of the physician who withholds treatment is a heavy one The inadequate ophthalmologic data provided by most of the investigators in this field make it impossible to draw accurate conclusions as to the probable success or failure of any treatment method in a given case,

TABLE 11

The material of various investigators shows better results in early than in advanced optic atrophy

VISION IN THE BETTER EYE BEFORE TREATMENT	TOTAL CASES	AVERAGE PERIOD OF OBSERVATION	RESULTS OF TREATMENT	
			Improved or stationary	Worse
20/40–20/20	17	3 years	10	7
Less than 20/40 but not worse than finger movements	11	2⅓ years	4	7

except on the basis of the degree of visual failure present If one analyses the reports of Schacherl, Zimmermann, Lederer, and Hessberg, one arrives at the data shown in table 11 Here is confirmed the *a priori* conclusion that the earlier treatment can be started, the better the result Of 17 patients in whom vision in the better eye was 20/40 or more, the process was arrested in 10, or 58 per cent, while among 11 patients in whom vision in the better eye was less than 20/40, good results were obtained in only 4, or 36 per cent These figures combine the results of subdural and fever therapy

Enough has been said to make it quite clear that it is useless to expect any result from routine anti-syphilitic treatment Bismuth, mercury, or the iodides will not impede the progress of nerve degeneration in the slightest. It is unwise to employ them as Stokes suggests,

as preparation for subsequent arsphenamine, in the effort to avoid a Jarisch-Herxheimer reaction By doing so, valuable time may be lost, and further visual failure which cannot be remedied may occur The various subdural methods of treatment described all involve the use of intravenous arsphenamine, and in a small number of cases, the first injection of this drug may produce a Herxheimer reaction and rapid visual failure This usually occurs, as already pointed out, in patients with far advanced and rapidly progressing atrophy In any case, it is a risk worth accepting, since without treatment blindness is certain in any event

From the purely ophthalmologic standpoint, one may summarize the situation as follows subdural treatment, probably best given by the intracisternal route, offers something better than an even chance of arrest of the process provided vision in the better eye is 20/40 or more If it is less than this, the chance of preservation of useful vision is considerably less, but the attempt is still worthwhile as long as any vision better than light perception persists There is only a small risk that this form of treatment will accelerate the visual failure Malaria, or other forms of fever therapy, had better be reserved as a last resort, to be used in patients whose vision has continued to fail under subdural treatment, or who, for one reason or another, cannot be given arsphenamine products Malaria is somewhat less likely to bring about arrest of the process than subdural treatment, sufficient time has not yet elapsed to make it sure that the arrest produced by it is as lasting as that following subdural treatment, it is much more likely suddenly to accelerate the rate of visual failure than the subdural method, and it carries with it a distinct hazard to the life of the patient

It must be borne in mind, however, that the choice of a treatment method often depends, not on the ophthalmologic status, but on the evidences of syphilitic involvement of other portions of the nervous system than the optic nerves, or of other parts of the body than the nervous system, or on the presence of complicating non-syphilitic diseases Each patient represents an individual problem, to be solved by the combined efforts of the ophthalmologist and the syphilologist

SUMMARY

The unsettled problems of the syphilitic optic atrophies involve the clinical differentiation of their various forms, their incidence, early diagnosis, mechanism of development, pathology, and treatment About 90 per cent of the syphilitic optic atrophies are of the primary type, and syphilis outnumbers all other causes combined in the etiology of primary optic atrophy. Apparently primary optic atrophy may occur in association with various types of neurosyphilis, most commonly with tabes dorsalis It may be due to the pressure of syphilitic inflammatory tissue upon and resulting nutritional disturbance in, the optic conduction pathways, as from orbital gumma or periostitis, or from basilar meningitis It may occur as an almost isolated phenomenon in neurosyphilis, without associated clinical evidence either of tabes or of meningitis.

It is estimated that about 50,000 patients with syphilitic primary optic atrophy are constantly present in the United States

The diagnosis of primary optic atrophy cannot be made with certainty on the basis of pallor of the optic discs, which may not parallel the degree of visual improvement Alterations in the visual fields, and in the phenomenon of dark adaptation, both of which probably precede changes in the color of the disc, are more important elements in diagnosis Nothing is as yet known as to the incidence of these abnormalities in an unselected series of patients with neurosyphilis, nor of their prognostic importance when their appearance precedes subjective symptoms of visual failure Since hope in the treatment of optic atrophy depends on early diagnosis, however, close cooperation between syphilologist and ophthalmologist, and the routine ophthalmologic study of every patient with neurosyphilis, in order to arrive at a presumptive or definite early diagnosis before the development of visual failure, seems essential

The course of untreated primary optic atrophy is so variable as to render unsafe any conclusions as to the beneficial effects of treatment in the individual patient The process is practically always bilateral, though one eye may be involved weeks or months before the other The average time from onset of symptoms to blindness is 2 to 3 years, with extremes ranging from a few weeks to many years Spontaneous

temporary remission may occur, but ultimate blindness in untreated patients is inevitable

Many detailed studies of the pathology of optic atrophy have been made They have definitely established only one fact, namely, that the process begins in the marginal fibres of the optic nerve distal to the chiasm The degenerative process apparently bears no direct relationship to the presence or absence of exudative or inflammatory changes in the overlying or neighboring meninges or in the connective tissue septa of the nerve, or to the presence or absence of *T pallida* in or close to the visual pathways Pathologic studies of early optic atrophy are difficult to obtain and are largely lacking Theories of the development of primary atrophy are discussed, none of which as yet offer a completely satisfactory explanation of its mechanism

Attempts at the experimental production of syphilitic optic atrophy in laboratory animals have been unsuccessful

The treatment of primary optic atrophy in the pre arsphenamine era was unsatisfactory The introduction of the arsphenamines did not materially improve this situation Patients treated with an intravenous arsphenamine, bismuth, mercury, and the iodides in any combination and for any length of time appear to become blind about as rapidly as if nothing had been done Subdural treatment, with arsphenaminized serum, neoarsphenamine or bichloride of mercury dissolved in salt solution or spinal fluid, mercurialized serum, or air, injected intraspinally or intracisternally, has, however, been found to be of some value in the hands of many observers Various techniques of treatment are described In general, arrest of the atrophic process or even slight improvement may be accomplished in about 50 per cent of patients with early optic atrophy by the prolonged application of this method of treatment Patients most suitable for treatment are those in whom the atrophic process is still unilateral, or in whom visual acuity in the better eye is not worse than 20/40

The results obtainable from subdural treatment are sufficiently encouraging to justify its more widespread and patient trial That the method is not yet in more general use depends on many factors, perhaps the most important of which are that reports so far published are based on small numbers of patients followed for relatively short

periods of time, and that most of them lack convincing ophthalmologic data

Fever therapy, chiefly with malaria, has also been found by some observers to be of value in arresting the progress of optic atrophy, though these favorable opinions are offset by the unsatisfactory experience of others As yet, fever therapy is to be regarded as in the experimental stage The percentage of favorable results obtained from its use is lower than from subdural treatment, and treated patients have been followed for inadequately short periods of time Malaria has been noted to precipitate sudden visual failure during its course, and is, moreover, attended with some risk to life

Tryparsamide is absolutely contraindicated in the treatment of the syphilitic optic atrophies

The choice of a treatment method in the optic atrophies due to syphilis depends on a thorough general study of the patient The association of other lesions of syphilis in the nervous system or in the body elsewhere than the nervous system, or of complicating diseases, will often be the determining factors Each patient represents an individual problem calling for expert care and the closest cooperation between ophthalmologist and syphilologist

REFERENCES

ABADIE, C H , Traitement de l'atrophie tabétique des nerfs optiques, La Clin Ophth , 15, 313, 1926

ARLT, E , Behandelte und unbehandelte Falle von tabischer Sehnervenatrophie, Ztschr f artzl Fortbild , 19, 367, 1922

BEHR, C , The Treatment of Tabetic Optic Atrophy, Am J Ophth , 33, 240 and 263, 1916

BEHR, C , Ueber die Ernahrung des Sehnerven in physiologischer Beziehung und als Ursache der Unheilbarkeit der tabischen Sehnervenatrophie, Klin Monatsbl f Augenhk , 59, 241, 1917

BEHR, C , Ueber Metalues des Auges, Ztschr f Augenhk , 60, 319, 1926

BEHR, C , Ueber die anatomische Grundlagen und uber die Behandlung der tabischen Sehnervenatrophie, Munch Med Woch , 73, 311 and 366, 1926

BERING, FR , Die Behandlung der Tabes mit Malaria, Deut Med Woch , 52, 1611, 1926

CADY, L D , AND ALVIS, B Y , The Use of Tryparsamide in Patients with and without Ocular Lesions, J A M A , 86, 184, 1926

CHAMBERS, S O , Review of Literature on Treatment of Syphilitic Eye Disease, Arch Ophth , 57, 412, 1928

DWORJETZ, M , Ueber die Berechtigung der Bezeichnungs "Atrophia Nervi Optici," Klin Monatsbl f Augenhk , 80, 30, 1928

ELSCHNIG, A , Therapie der tabischen Sehnervenatrophie, Klin Monatsbl f Augenhk , 75, 773, 1925

FAZAKAS, R , Neuere Gesichtspunkte in der Behandlung der Atrophia nervi optici tabetica mittels endolumbaler und subokzipetaler Pneumokephalie, Klin Monatsbl f Augenhk., 83, 297, 1929

FISCHER ASCHER, M , Luesbehandlung und tabische Sehnervenatrophie, Med Klin , 22, 1991, 1926

FISCHER ASCHER, M , Malariabehandlung der tabischen Sehnervenatrophie, Klin Monatsbl f Augenhk , 76, 102, 1926

FLEISCHER in discussion of PLAUT, Zur Infektionsbehandlung der Metasyphilis, Ztschr f Augenhk , 61, 355, 1929

FORDYCE, J A , Results of Treatment in Syphilis of the Nervous System, Brit J Derm and Syph , 36, 47, 1924

FRIEDENWALD, J , Pigmentary Degeneration of the Retina in Cerebrospinal Syphilis, Am J Ophth , 13, 943, 1930

FUCHS, A , Liquor und Sehnervenveränderungen bei Syphilis, Ber u d Versamml Deutsch Ophth Gesellsch , 43, 146, 1921

FUJIWARA, K , Ein Beitrag zur Kenntnis der pathologischen Anatomie des Sehnervenschwundes bei Tabes Dorsalis und progressiver Paralyse, Arch f Ophth , 115, 562, 1925

GENNERICH, W , Die Syphilis des Zentralnervensystems, Julius Springer, Berlin, 1921

GERSTMANN, J , Die Malariabehandlung der Progressiven Paralyse, Julius Springer, Wien, 1925

GIFFORD, S R , AND KEEGAN, J J , Results with Intracisternal Injections in Luetic Optic Atrophy, Am J Ophth , 10, 323, 1927

GILBERT, W , Behandlung der tabischen Sehnervenatrophie und der Keratitis Parenchymatosa, Med Klin , 25, 235, 1929

GREEF, Zur Therapie der tabischen Sehnervenatrophie, Ber d Deut Ophth Ges , 43, 133, 1920

HARMAN, N B , Discussion on the Etiology of Optic Atrophy, Brit M J , 2, 1161, 1922

HASSIN, G B , Tabes Dorsalis, Pathology and Pathogenesis, Arch Neur and Psych , 21, 311, 1929

HAUPTMANN, A , Ausbau meiner Metalues Theorie auf Grund neuerer Forschungser gebnisse, Ztschr f d ges Neur u Psych , 128, 107, 1930

HAVEL, J , Malariabehandlung der tabischen Sehnervenatrophie, Casopis lékařu českých, 67, 1055, 1928, abstr in Zentralbl f d ges Ophth , 20, 610, 1929

HAWTHORNE C O , Discussion on the Etiology of Optic Atrophy, Brit M J , 2, 1153, 1922

HEAD, H , AND FEARNSIDES, E G , The Clinical Aspects of Syphilis of the Central Nervous System in the Light of the Wassermann Reaction and Treatment with Neosalvarsan, Brain, 37, 1, 1914

HESSBERG, R , Weitere Ergebnisse der Fieberbehandlung luetischer insbesondere tabischer Sehnervenerkrankung Monatsbl f Augenhk , 84, 261, 1930

HORN, L , AND KOGERER, H , Ueber die Ergebnisse der Nachuntersuchung der mit Lufteinblasung behandelten Fälle von tabische Opticus Atrophie, Ztschr f Augenhk , 67, 207, 1929

HORN, L , AND KAUDERS, O , Eine neue Methode der abgeschwachten Malariabehandlung, Wien, Klin Woch , 41, 585, 1928

IGERSHEIMER, J , Syphilis und Auge, Julius Springer, Berlin, 1918

IGERSHEIMER, J , Ueber der Opticusprozess bei Tabes und Paralyse, Deut Med Woch , 52, 943, 1926

IGERSHEIMER, J , Syphilis und Auge, Ergebn, d allg Path u Path Anat , 21, 34, 1928

INGVAR, S , On the Pathogenesis of the Argyll-Robertson Phenomenon, J H Hosp Bull , 43, 363, 1928

JAENSCH, P A , Zur Therapie des Tabischen Sehnervenschwundes, Ztschr f Augenhk , 71, 12, 1930

JAHNEL, F , Die Spirochaeten im Zentralnervensystem bei der Paralyse, Ztschr f d ges Neur u Psych 73, 310, 1921

JOHN, I , Ueber die Haufigkeit der tabischen Optikusatrophie und uber die bisherigen Behandlungsmethoden, Ztschr f Augenhk , 69, 283, 1929

KEIDEL, A , AND MOORE, J E , The Treatment of Neurosyphilis by the Intraspinal Route, J H Hosp Bull , 31, 404, 1920

KEMP, J E , Syphilis of the Orbit, Arch Derm and Syph , 8, 165, 1923

LECOUNT, E R , AND DEWEY, K , Syphilitic Leptomeningitis, J Inf Dis , 16, 142, 1915.

LEDERER, R , Ein Versuch, den Verlauf des tabischen Sehnervenschwundes zu beeinflussen, Ztschr f Augenhk , 64, 50, 1928

LEVADITI, C , SANCHIS-BAYARRI, M J , AND SCHOEN, R , Le Virus Syphilitique comporte-t-il un cycle évolutif dont le Tréponema pallidum n'est qu'une des phases connues? Ann de l'Inst Past , 42, 475, 1928

LILLIE, W I , Syphilis of the Central Nervous System, observations from an Ophthalmologic Standpoint, J A M A , 83, 809, 1924

MATTAUSCHEK, E , AND PILCZ, A , Zweite Mitteilung uber 4134 Katamnestisch verfolgte Falle von luetischer Infektion, Ztsch f d ges Neur u Psych , 15, 608, 1913

MEESMAN AND ROGGENBAU, Ergebnisse der kombiniert endolumbale, intramuskular-intravenosen und der Malariabehandlung der tabischen Opticusatrophie, Proc of XIII Int Cong of Ophth , Amsterdam, 1929, abstr in Zentralbl f d ges Ophth , 22, 812, 1930

MOORE, J E , ROBINSON, H M , AND KEIDEL, A., Tryparsamide in the Treatment of Syphilis, J A M A , 82, 528, 1924

MOORE, J E , The Treatment of Central Nervous System Syphilis, J A M A , 89, 588, 1927

NOGUCHI, H , AND MOORE, J. W , A Demonstration of Treponema Pallidum in the Brain in Cases of General Paralysis, J Exp Med , 17, 232, 1913

NOGUCHI, H , Studien uber den Nachweis der Spirocheta pallida in Zentralnervensystem bei der progressiven Paralyse und bei Tabes dorsalis, Munch Med Woch , 60, 737, 1913

NONNE, M , Metalues des Sehorgans, Ztschr f Augenhk , 60, 335, 1926

O'LEARY, P , AND BRUNSTING, L A , The Non-specific Treatment of Neurosyphilis, Fifth Annual Report, J A M A , 94, 452, 1930

PACHECO E SILVA, A C , AND CANDIDO DA SILVA, Nachweis der Treponema pallidum im Sehnerv, Mem do hosp du Juquery, 3–4, 29, 1927, abstr in Zentralbl f d ges Ophth , 20, 850, 1929

PALICH-SZANTO, O , Beitrage zur Atiologie und Pathohistologie der tabischen Sehnervenatrophie, Arch f Augenhk , 82, 48, 1917

PETTE, H , Weitere klinische und pathologische anatomische Beiträge zum Kapitel der Frühlues des Zentralnervensystem, Ztschr f d ges Neur u Psych , 92, 346, 1924

RICHTER, H , Zur Histogenese der Tabes, Ztschr f d ges Neur u Psych , 67, 1, 1921

RICHTER, H , Einige Bemerkungen zur Pathogenese der Tabes, Arch f Psych , 72, 318, 1924

ROTTER, R , Erfahrungen mit der Salvarsan Eigenserumbehandlung bei den syphilogenen Erkrankungen des Gehirns und Rückenmarkes, Arch f Psych , 90, 824, 1930

SABBADINI, D , AND PISANI, D , Sulle modificazioni delle lesioni oculari metaluetische con la malarioterapia, Riv oto neuro oftal , 4, 682, 1927, abstr in Arch Neur and Psych , 20, 620, 1928

SALEEBY, E , AND GRLEBBAUM, S , Comparative Biologic and Histologic Study of Lymph Glands from Syphilitic Patients, J A M A , 96, 98, 1931

SCHACHERL, M , Ergebnisse endolumbaler Salvarsanbehandlung bei tabischer Opticusatrophie, Deut Ztschr f Nervenhk , 77, 234, 1923

SCHACHERL, M , Therapie der organischen Nervenkrankheiten, Wien, Julius Springer, 1927

SCHINDLER, F , Ueber die klinische Bedeutung der Dunkeladaptation, Klin Monatsbl f Augenhk , 68, 710, 1922

SCHOENBERG, M J , Intracranial Treatment of Syphilitic and Parasyphilitic Optic Nerve Affections, J A M A , 66, 2054, 1916

SCHOENBERG, M J , Remarks on Diagnosis and Treatment of Luetic Involvement of the Optic Pathways, Arch Ophth , 49, 203, 1920

SCHWAB, S I , AND CADY, L D , The Use of Tryparsamide in Neurosyphilis, Am J Syph , 11, 1, 1927

SOMBERG, J S , Optic Nerve Pallor without Functional Disturbances in Luetics, Am J Ophth , 10, 837, 1927

SPIELMEYER, W , Die Trypanosomenkrankheiten und ihre Beziehungen zu den syphilogenen Nervenkrankheiten, Gustav Fischer, Jena, 1908

SPIELMEYER, W , Zur Pathogenese der Tabes, Ztschr f d ges Neur u Psych , 84, 257, 1923

SPIELMEYER, W , Pathogenese der Tabes und Unterschiede der Degenerationsvorgänge im peripheren und zentralen Nervensystem, Ztschr f d ges Neur u Psych , 91, 627, 1924

STARGARDT, Ueber die Ursachen des Schnervenschwundes bei der Tabes und der progressiven Paralyse, Arch f Psych u Nervenkr , 51, 711, 1913

STERN, R O , A Study of the Histopathology of Tabes Dorsalis with special reference to Richter's Theory of its Pathogenesis, Brain, 52, 295, 1929

STOKES J H , AND SHAFFER, L W , Results Secured by Standard Methods of Treatment in Neurosyphilis, J A M A , 83, 1826, 1924

STOKES, J H , AND SHAFFER, L W , Clinical Management and Response of the Tabetic Patient, J A M A , 85, 1271, 1925

STOKES, J H The Principles of Syphilotherapy as Applied to the Eye, Arch Ophth , 56, 229, 1927

SWIFT, H F , AND ELLIS, A W M , The Direct Treatment of Syphilitic Disease of the Central Nervous System, N Y Med Jour 96, 52, 1912

SWIFT, H F , Intraspinal Therapy in Syphilis of the Nervous System, J A M A , 65, 209, 1915

SWIFT, H F , A Study of Serum Salvarsanized in Vitro, J Exp Med , 24, 373, 1916
TRAQUAIR, H M , The Clinical Differentiation of the Various Forms of Optic Atrophy, Brit M J , 2, 1157, 1922
USILTON, L J , Prevalence of Venereal Disease in the United States, Ven Dis Inform , 11, 543, 1930
VERSÉ, M , Ueber das Vorkommen der Spirocheta pallida bei früh- und spätzyphilitischen Erkrankungen des Zentral nervensystems, Munch Med Woch , 60, 2446, 1913
VINER, N , AND MCMURTRY, S O , The Arrest of Luetic Optic Atrophy by Cisternal Injection of Mercury, Can Med Ass J , 15, 910, 1925
VRANEŠIČ, G , Liquormechanik und endolumbale Behandlung intrakranieller Prozesse, Arch f Psych , 90, 1, 1930
WAGNER-JAUREGG, Ueber tabische Optikus atrophie und deren Behandlung, Ztschr f Augenhk , 61, 127, 1927
WARTHIN, A S , AND OLSEN, R E , The Granular Transformation of Spirocheta Pallida in Aortic Focal Lesions, Am J Syph , 14, 433, 1930
WILBRAND, H , AND SAENGER, A , Neurologie des Auges, J F Bergmann, Wiesbaden, 5, 518, 1913
WINKLER, L , Ueber Schwefeltherapie der optikus Atrophie, Wien Klin Woch , 41, 374, 1928
WOLFF, J , Behandlung der Atrophia Nervi Optici durch Malariakuren und Pyrifer-injektionen, Proc of XIII Int Cong of Ophth Amsterdam 1929, abstr in Zentralbl f d ges Ophth , 22, 812, 1930
WOODS, A C , AND DUNN, J R , Etiologic Study of a Series of Optic Neuropathies, J A M A , 80, 1113, 1923
WOODS, A C , AND MOORE, J E , Visual Disturbances Produced by Tryparsamide, J A M A , 82, 2105, 1924
WOODS, A C , AND ROWLAND, W M , An Etiologic Study of a Series of Optic Neuropathies, J A M A , 97, 375, 1931
WURZ, J , Zur Therapie der tabischen Sehnervenatrophie mit Typhusvakzine, Zweite Tagung der Tschecho-Slov Ophth Ges , Prag, 1927, abstr in Klin Monatsbl f Augenhk , 79, 127, 1927
ZIMMERMANN, E L , The Treatment of Tabetic Optic Atrophy, Arch Ophth , 54, 545, 1925
ZIMMERMANN, E L , The Role of the Arsphenamines in the Production of Ocular Lesions, Arch Ophth , 57, 509, 1928

EXPERIMENTAL EPIDEMIOLOGY[1]

LESLIE T WEBSTER, M D

From the Laboratories of The Rockefeller Institute for Medical Research, New York

Some intensive experimental work in epidemiology has been in progress during the past twelve years It was commenced at a time when the theories of communicability and microbic etiology of certain epidemic diseases were widely accepted, when the events of infection were described in terms of microbic virulence, dosage, and host resistance, and when epidemic outbreaks were attributed for the most part to enhancement of virulence and their abatement to loss of virulence and to acquisition of specific resistance by the host Already these theories were being criticized In the first place, the discovery of "healthy" carriers indicated that disease and epidemics especially must be due to something more than mere exposure of host to virulent microorganisms Again the old ideas that the inherent resistance of the host, diet, climate, and season act to influence in some manner the spread of infection were being reinforced by recent observations Most important, however, was the realization that the old established techniques of epidemiology, bacteriology, and immunology had failed to yield the data necessary to solve the remaining problems of epidemiology The descriptive epidemiologist, for example, was submitting to mathematical analysis vital statistics containing gross uncontrolled sources of error, the bacteriologist was studying the problem of virulence in artificial infections and artificial media without determining whether his findings are especially related to the behavior of microorganisms in their native host, and the immunologist was gaining knowledge of the specific substances found in the blood of individuals who have been exposed to microorganisms without investigating thoroughly the extent to which these specific substances are related to the resistance of the host under natural conditions In short, experimental evidence was not forthcoming to answer the question of whether

[1] Harvey Lecture, 1932

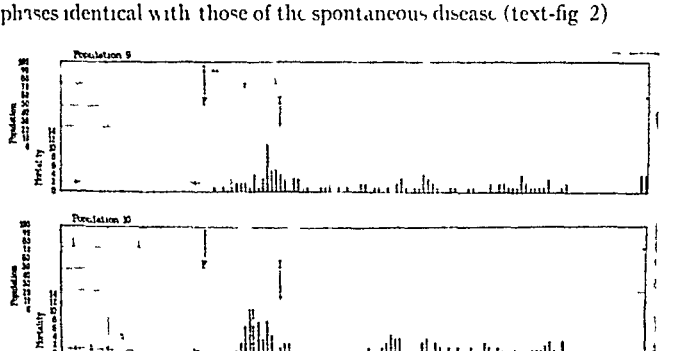
responded in like manner, and that titrations to measure virulence, dosage, and resistance carried out in duplicate and quadruplicate, and repeated at short intervals gave results varying less than 10 per cent (text-fig 1)

To summarize, a technique has been evolved which is quantitative and yet reproduces the natural phenomena of infection, which permits critical observations on the questions of whether microbic and host factors account for all the mass phenomena of infectious disease, and if so, in what manner these variables function

The data provided by the method of experimental epidemiology will be considered with reference to five major findings One is that all the phenomena of infection studied thus far experimentally can be described completely in terms of microbic and host factors Another is that microbic virulence, although potentially variable, is under natural conditions relatively stable A third is that microbic dosage varies with the amount and severity of infection, increasing prior to outbreaks and decreasing prior to subsidence of infection A fourth finding is that breeds and individuals possess definite and different amounts of non-specific inherited resistance to infection, that this resistance is affected by environmental factors, such as season and diet and may be supplemented by a specific immunity Finally, it developed that the amount of resistance present in individuals or populations at a given time determines largely the extent and severity of disease These results will now be considered in detail

Early experiments showed that natural infection could be established in a susceptible population by administering pure cultures of specific bacteria to constituents or to immigrants Amoss, in 1922 (3), fed mouse typhoid cultures to ten mice and placed them in two cages in the midst of 100 normal mice in twenty cages All were fed by the same attendant who went from cage to cage The specific infection proved fatal to eight of the ten and spread to the normal animals Later, four batches of mice were added and the infection extended to each group in turn In our laboratory in 1930 (4) Friedlander pneumonia was established in four populations of mice by administering 500 bacilli intranasally to certain individuals In one experiment the entire group received the organisms and healthy immigrants were added thereafter at the rate of two per day for three

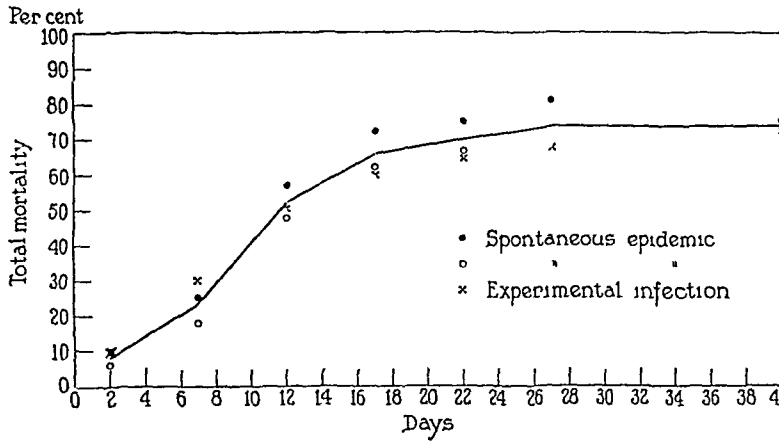
and a half years In two further experiments three groups of 100 mice each received 6 immigrant mice which had been given 500 Friedlander bacilli intranasally Healthy immigrants were added thereafter for two and a half years and eight months respectively In each case the Friedlander infection spread from the immigrants to the healthy population and became established with endemic and epidemic phases identical with those of the spontaneous disease (text-fig 2)



TEXT FIG 2 EPIDEMICS OF *B friedlanderi* PNEUMONIA FOLLOWING INTRODUCTION OF CARRIERS INTO EXPERIMENTALLY CONTROLLED POPULATIONS OF HEALTHY ROCKEFELLER INSTITUTE STRAIN MICE

Early experiments likewise showed that epidemics could be induced in populations under two sets of conditions First, by administering to each individual of previously unexposed communities a certain dose of the specific organisms by way of the natural portal of entry, and second, by adding susceptible immigrants to already infected populations Epidemics of mouse typhoid were incited in previously unexposed populations by administering three to five million bacilli in broth intrastomachally to batches of 20 to 100 mice The resulting mortality over a sixty day period in averaged tests was characteristic and practically identical with that occurring during spontaneous

epidemics (text-fig 3) Epidemics of Friedlander pneumonia were incited in previously unexposed populations by administering 500 bacilli in broth intranasally to batches of 50 to 100 mice The resulting mortality over a thirty-day period was uniform in averaged tests and similar to that occurring during spontaneous epidemics (text-fig 4) In infected populations, outbreaks of mouse typhoid were incited by adding batches of normal susceptible immigrants Following some suggestive observations of Topley in 1919 (1), Amoss assembled 100 healthy mice in twenty cages of 5 mice each and placed in their midst two additional cages of 5 mice each, which had been fed on a culture of mouse typhoid bacilli (5) Four weeks later forty

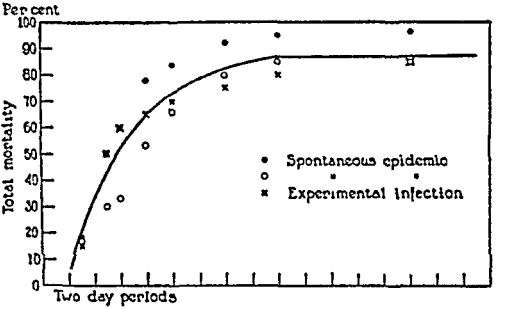


TEXT-FIG 3 COMPARISON OF MORTALITIES IN SPONTANEOUS EPIDEMICS (5) AND EXPERIMENTAL INFECTION (6) *B aertrycke* MOUSE TYPHOID

additional cages, containing 5 mice each, were placed next the first batch Subsequently, sporadic infection occurred, fatal in three months to about 50 per cent of the population The survivors were recruited to their original numbers by replacements to maintain 5 mice in each cage Within a few days an epidemic of mouse typhoid occurred, fatal to 70 per cent of the population in two months A second and a third replacement were made, followed by outbreaks of decreasing severity These results were confirmed in 1925 by Greenwood and Topley (8), who showed that the repeated addition of normal individuals to mouse populations infected with Pasteurella is followed by recurring epidemic waves Likewise, experiments at the

Rockefeller Institute in 1930 (4) showed that if immigrants were added to one of three mouse populations infected with *B friedlanderi*, recurrent epidemics of pneumonia ensued, while if at the same time and under identical conditions, immigrations were discontinued in the two remaining populations, no epidemics occurred and the infection died out

Topley and Greenwood, in further observations on infected mouse populations (8), emphasized the close association between mortality and the number of susceptible immigrants They found that when mice were added to an infected community at a constant rate, the



TEXT FIG 4 COMPARISON OF MORTALITIES IN SPONTANEOUS EPIDEMICS (4) AND EXPERIMENTAL INFECTION (7) *B friedlanderi* MOUSE PNEUMONIA
Reprinted from *J Exp Med*, 1930, 52, 918

mortality was propagated in regularly recurrent waves and suggested that the character of the waves was dependent upon the rate of addition of immigrants We observed later that when four or more populations of mice infected with *B friedlanderi* (4) were recruited at the rate of 2 mice per day, the primary epidemic waves of pneumonia occurred when the population had reached a certain level, lasted a definite number of days, and reduced the number of animals to a definite low level Moreover, when *B enteritidis* typhoid was spreading under identical conditions in uncomplicated form in these communities (9), the mortality waves occurred with considerable regularity at nine- to eleven day intervals It is plain that epidemics can be

incited in already infected herds by the addition of susceptible immigrants in suitable numbers, and in unexposed populations by administering to each individual a certain dose of the specific organisms

Early in these studies, Topley observed that, following epidemics of mouse typhoid, there are a certain number of survivors, and he stated that these survivors are both potentially infective and relatively immune (10) Evidence of the immunity of survivors was obtained later in our laboratory by actually comparing the resistance of surviving and non-exposed mice (11) Mouse typhoid organisms were administered by mouth to 100 individuals, sixty days later there were thirty-two survivors These, together with 20 normal unexposed mice, were then given a similar dose of bacteria Sixty days later 30 per cent of the survivor group had succumbed, as compared to 80 per cent of the control group, showing that by actual test, survivors are more resistant than non-exposed animals

The results thus far described demonstrate that various endemic and epidemic phenomena of natural enteric and respiratory infection can be elicited experimentally solely by bringing together susceptible hosts and pathogenic microorganisms, thus furnishing additional experimental evidence for the infection hypothesis brought forward by the Pasteur-Koch school fifty years ago Another accomplishment of these experiments has been to afford an opportunity for analyzing the microbic and host factors under natural, yet controlled, conditions, and of determining whether virulence actually varies during epidemics and whether epidemics are brought to an end by the population acquiring a specific immunity

The question of the virulence factor will first be considered The assumption that the virulence of a microorganism, its capacity to harm its native host, is a highly labile variable is derived from the early observations of Davaine and Pasteur Supported by later bacteriologists, it has come to form the basis of modern epidemic theory The experimental epidemiologist, however, recognizing that it is derived from tests which are now regarded as inadequate, has interested himself in the virulence of bacteria under conditions as nearly natural as possible

In one series of experiments, typical strains of organisms from infected animals were found to be of uniform virulence, whether re-

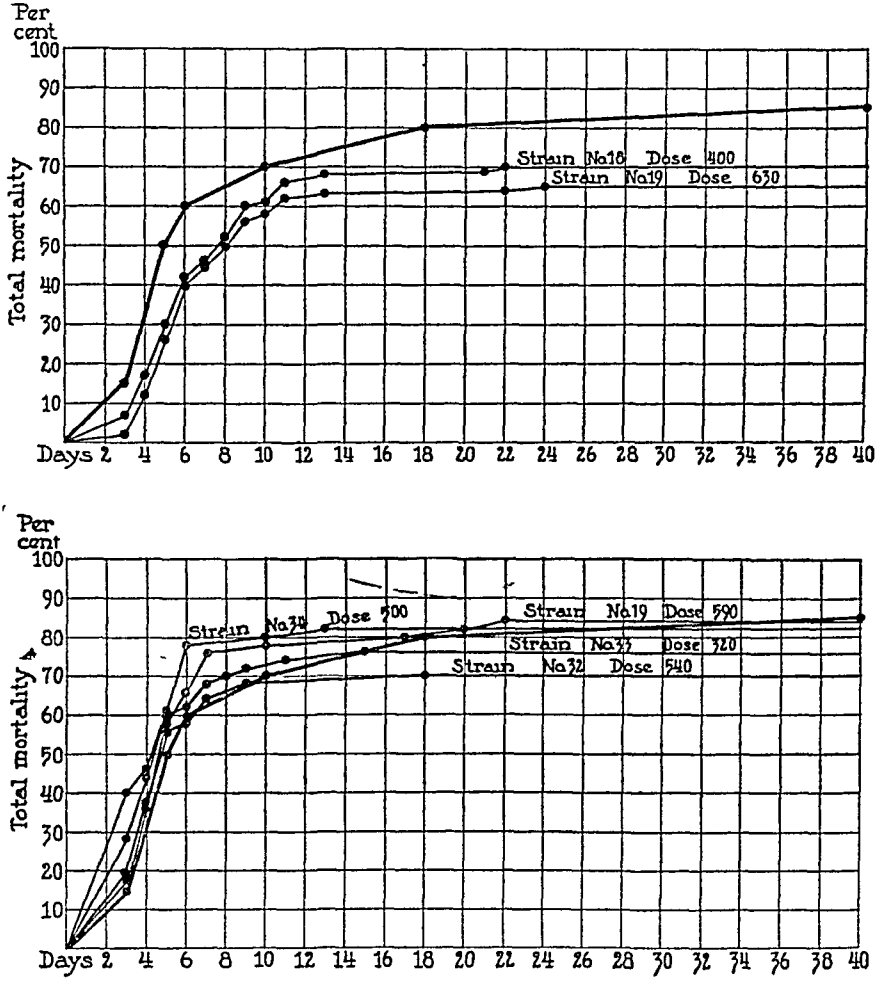
covered early or late in the course of disease (12) For example each of two cultures of mouse typhoid organisms were given intrastomachally to 20 mice, one from the heart's blood of an animal dying with acute septicemia five days after exposure to mouse typhoid, the other from the blood of a mouse with chronic septicemia, alive and apparently healthy five weeks after exposure The acute septicaemic culture proved fatal to fourteen, the chronic septicemic culture to 12 mice

Other tests showed that strains of mouse typhoid, Friedlander, and fowl cholera organisms from healthy carriers were in general of the same virulence as strains recovered from fatal cases Thus, each of three strains of *aertrycke* mouse typhoid organisms was given by mouth to 20 mice, one a culture from an acute septicemic case, two others from stools of 2 mice surviving and healthy five weeks after exposure The mortalities were 70, 70, and 65 per cent, respectively (12) Tests with *B enteritidis* mouse typhoid gave similar results (9) Several strains of mouse Friedlander organisms were administered intranasally to batches of 50 or 100 mice in comparable doses (4) In one instance, a culture from the lung of a fatal case was compared with a culture obtained from the nasal passages of a healthy carrier Each was given to 100 mice intranasally The resulting mortalities were 70 and 65 per cent, respectively Tests were made with thirty fowl cholera strains from fatal cases and forty strains from healthy carrier fowl on several commercial farms (13) Each strain was administered into the nasal cleft of twenty specially bred young birds In general, strains from fatal cases proved to be of the same virulence as similar strains from healthy carriers

Further experiments indicated that strains of specific organisms recovered from a given population at various endemic and epidemic periods of spontaneous infection were of uniform virulence. Epidemics of fowl cholera (13) and rabbit-snuffles pneumonia (14, 15), mouse typhoid (9) and mouse pneumonia (4) (text fig 5) were studied in the Rockefeller Institute Laboratory, epidemics of guinea pig and rabbit Pasteurella and pneumococcus pneumonia by Neufeld and Freund (16), and epidemics of guinea pig typhoid by Theobald Smith and Nelson (17) In no instance were significant differences in the virulence of pre-epidemic, epidemic, and post epidemic strains detected

Still other tests showed that strains of the same organisms from

different populations may differ in virulence and in general that the strains with high initial killing potency possessed relatively little ability to persist in the tissues of survivors and vice versa This



TEXT-FIG 5 TITRATIONS OF VIRULENCE OF EPIDEMIC AND ENDEMIC STRAINS OF *B friedlanderi*

Strain 18 Carrier culture, healthy individual, inter-epidemic period Strain 19 Lung culture, fatal case, epidemic period Strain 32 Lung culture, fatal case, epidemic period Strain 33 Lung culture, fatal case, epidemic period Strain 34 Carrier culture, healthy individual, post-epidemic period

latter fact found illustration in experiments in which an epidemic or endemic strain of fowl cholera organisms was administered intranasally to young chickens and permitted to spread to healthy contacts

(18) The tendency of the epidemic strain to kill but not to persist in survivors or spread to contacts, in contrast to the tendency of the endemic strain to persist and spread but not to kill, was consistent The same differences were demonstrable with epidemic and endemic strains of rabbit Pasteurella (19)

The influence of bacterial dissociation on the prevalence of rabbit and fowl pasteurelloses, mouse *B enteritidis* and *B friedlanderi* infections has been studied In the case of rabbit pasteurellosis, virulent "S" strains of *P lepiseptica* were dissociated *in vitro* into "G" forms of low virulence (20) This was observed *in vivo* by giving rabbits virulent "S" strains intranasally and taking cultures from the nasal passages of survivors (21) From a few individuals, "G" forms were recovered for short periods of time However, if rabbits of a population in which pasteurellosis was spreading spontaneously were cultured from the nasal passages, "G" forms were seldom, if ever, present Only the virulent forms spread from animal to animal (22) The organisms of fowl pasteurellosis behaved in a similar manner (13–18) Virulent strains of *B friedländeri* associated with mouse pneumonia were dissociated *in vitro* into avirulent "G" forms (7) But during three years' observation on the spread of the disease in eight mouse populations, "G" forms were not found on carrier or autopsy cultures If the "S" forms disappeared from a community, the infection likewise died out (4) Finally, virulent strains of *B enteritidis* were dissociated *in vitro* by means of a highly potent bacteriophage associated with the spontaneous *B enteritidis* mouse typhoid infection (23) These "M" and "R" forms, however, neither persisted nor spread when administered *per os* to normal mice (24) And during four years' experience with eight infected mouse populations in which the bacteriophage was present in many autopsy cultures, the dissociated forms were encountered in rare instances and insignificant numbers (9) The virulent forms were responsible for the spread of the disease from host to host It is concluded, therefore, that microbic dissociation phenomena played no part in determining the prevalence of infections thus far studied

One further series of tests may be mentioned briefly—namely, those of the effect of animal passage on virulence Since the early days of bacteriology, cultures have been transferred from animal to

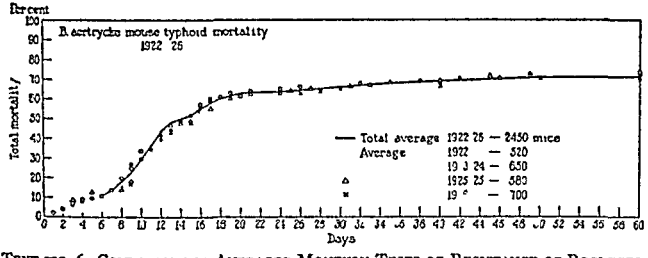
animal for the purpose of enhancing their virulence The tests have been made for the most part in some foreign animal host and by means of some artificial method, such as intraperitoneal injection, and the results, although definite in a few instances, have usually proved equivocal Nevertheless, they have been invoked to support the idea that prior to an epidemic the virulence of the specific agent increases by means of passage from host to host The present tests were made under conditions as nearly natural as possible Mouse typhoid organisms from heart's blood or intestinal contents of animals in the acute stages of infection were given intrastomachally to batches of mice without intermediate cultivation on artificial media Such passages were made serially and repeatedly, and at intervals titrations were made of the comparative virulences of the passed and unpassed strains (25) Similar tests were made with Pasteurella cultures native to rabbits (26), and fowl cholera organisms native to chickens (27) In no instance was a significant increase in virulence demonstrable

In summary, the effective virulence of a given strain of microorganisms, when analyzed under natural and controlled conditions, has proved to be a relatively stable property and in general inversely related to its ability to survive in the tissues of its natural host The virulence of strains of the same organism in the same community was uniform, while the virulence of strains from different communities was at times dissimilar

The next epidemic factor to be analyzed was that of microbic dosage —the number of organisms available to the individual host or to the total population at a given time The findings may be summarized as follows Changes in dosage exerted a direct effect upon mortality, when virulence and resistance were constant As dosage was increased, there ensued a progressive increase in percentage mortality up to a point less than 100 per cent Further increase in dosage had no effect on mortality Thus, in a titration of mouse Friedlander bacilli, each of eight doses of the organisms given intranasally to 25 mice resulted in mortalities of 32, 44, 56, 64, 88, 96, and 96 per cent, respectively (7) The second finding has been referred to before, namely, that by giving mice proper doses of typhoid or Friedlander organisms, it is possible to reproduce closely the events of explosive,

spontaneous epidemics (text-fig 4) Finally, as will be pointed out in tests referred to later, during the actual spread of infection in populations, dosage increased prior to epidemics and decreased prior to their decline by a time interval which approximated that of the incubation period of the infection (4–9)

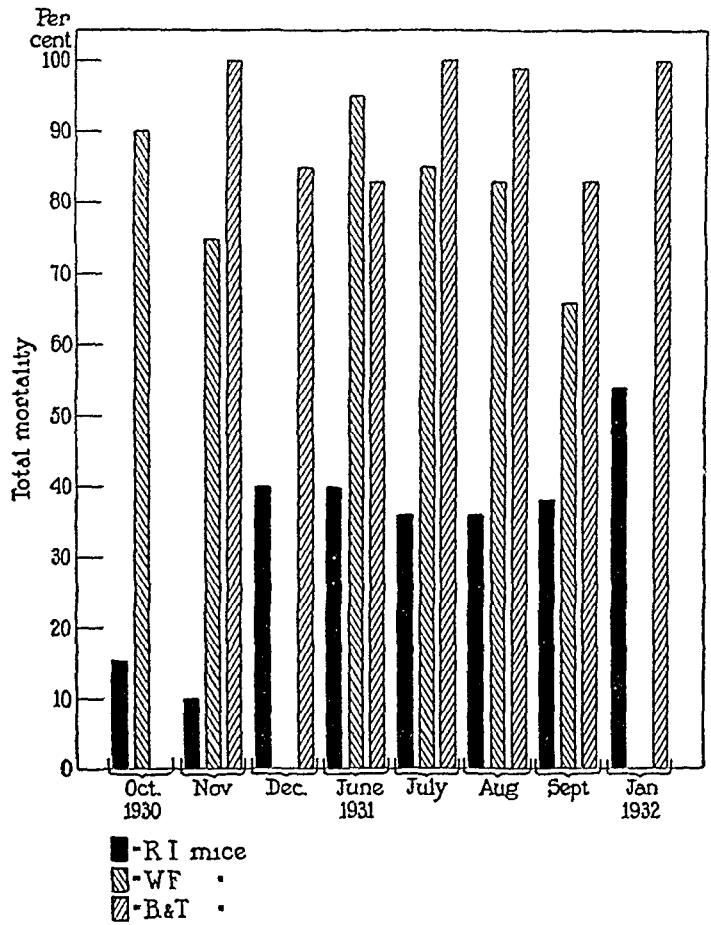
Host resistance, the third epidemic factor, was found to be made up of both non-specific and specific components The non specific component was present in certain definite amounts in breeds or races of animals For example, monthly tests of the resistance of an inbred strain of mice to mouse typhoid organisms were made from 1922 to 1926 The results in terms of mortality were averaged each year and found to approximate each other within 2 or 3 per cent (text-fig 6)



TEXT FIG 6 COMPARISON OF AVERAGED MONTHLY TESTS OF RESISTANCE OF ROCKEFELLER INSTITUTE STRAIN MICE TO INTRASTOMACHAL INSTILLATION OF 5,000,000 *B aertrycke* MOUSE TYPHOID ORGANISMS

Similar tests with other enteric infections and with respiratory ones, and tests with other strains of mice gave equally consistent results The non specific components of resistance were present in different amounts in different races or breeds Thus, a black Lathrop strain, pen inbred for twelve generations, proved on nineteen consecutive monthly tests with *B aertrycke* (28) and several consecutive tests with *B enteritidis* mouse typhoid (9) to be more susceptible than the Rockefeller Institute strain of mice Albino mice of Swiss strain, also highly inbred, and albino Rockefeller Institute mice were raised on four different diets In each case the Swiss mice proved more susceptible Repeated tests with white-faced (text-fig 7) and black and tan strains, brother and sister inbred, showed them to be more susceptible than the Rockefeller Institute line

The non-specific component of resistance was also proved to be present in different amounts in individuals of the same breed. Thus, when a controlled group of animals were all given the same, suitable dose of $HgCl_2$, individuals showed markedly different types of re-



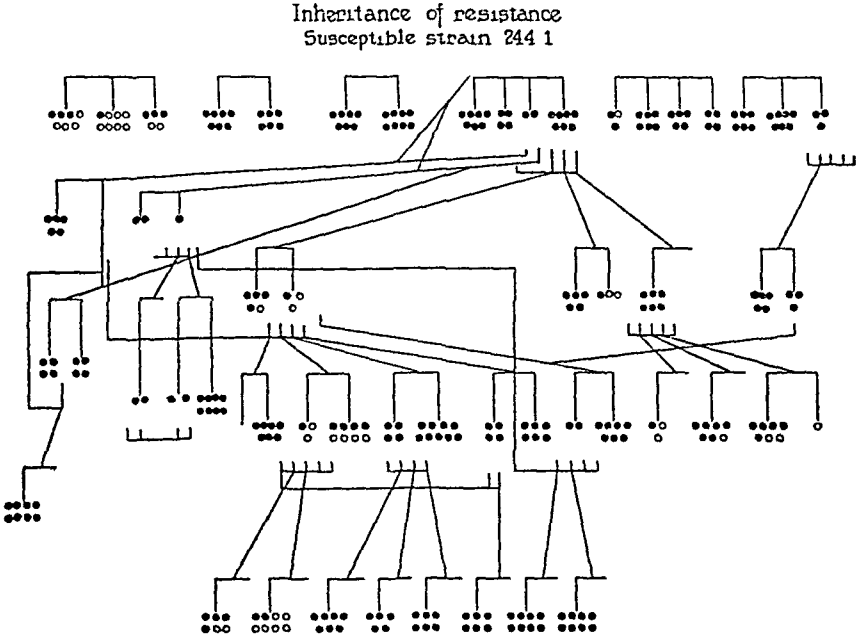
TEXT-FIG 7 COMPARATIVE MORTALITIES OF ROCKEFELLER INSTITUTE, WHITE-FACE, AND BLACK-AND-TAN STRAIN MICE TO INTRASTOMACHAL INSTILLATION OF 5,000,000 *B enteritidis* MOUSE TYPHOID ORGANISMS

sponse, ranging from death after the briefest interval to a completely refractory state (29) In the same way, when a group of animals previously unexposed were given a native infection by the normal portal of entry, using the same dose of microorganisms, individuals showed markedly different types of response, ranging from death

after the briefest incubation period to a completely refractory state These differences were more regular and predictable when every precaution had been taken to insure uniformity of inheritance, environmental conditions, and food In *B aertrycke* mouse typhoid, for example, when groups of mice were given bacilli intrastomachally, 70 per cent died with positive blood cultures in a period of five to sixty days, while 30 per cent survived Of these latter, about 20 per cent were recovered cases, with or without positive agglutinins, while 10 per cent showed no evidence of infection (12) Again, when rabbits were given a similar dose of Pasteurella intranasally, approximately 28 per cent died of pneumonia, of acute interstitial, lobar, or chronic empyema types, 44 per cent showed merely local rhinitis or sinusitis, 13 per cent became healthy carriers, and 14 per cent remained uninfected (19, 30) Similar individual differences were manifest after the administration of fowl cholera organisms to chickens These findings have been confirmed by workers in Neufeld's laboratory in their studies of Friedlander, Pasteurella, and pneumococcus infections of mice (31) In short, individuals submitted to precisely the same risk of infection, under identical conditions, with every known factor controlled, exhibit profound differences in response

That these differences in the reaction of individuals are due to a non-specific resistance which is inherited was shown by the results of tests on survivors and by breeding experiments Mice surviving an intrastomachal instillation of mouse typhoid organisms proved more resistant to an instillation of mercury bichloride than unselected mice of the same strain (11) The progeny of mice surviving *aertrycke* or *enteritidis* typhoid were more resistant to subsequent infection with mouse typhoid bacilli or to doses of mercury bichloride than normal, unselected mice of the same strain, and conversely, progeny of mice, succumbing early to typhoid, were more susceptible than unselected mice (32) A further study of the inheritance of different degrees of susceptibility is now in progress Five hundred female and 100 male mice of the Rockefeller Institute strain were mated, 1 male to 5 females When the young were weaned, the 600 parents were given intrastomachally three million *enteritidis* mouse typhoid bacilli In cases in which both parents died within ten days after infection and

in which, in contrast, both parents survived sixty days, the respective litters from susceptible and resistant parents were saved for further breeding Simultaneous tests of resistance have since been made on the progeny of six generations of the original susceptible and resistant groups together with an unselected control group The possibility of specific immunity developing from infected animals was definitely ruled out by testing the population for carriers, by testing animals

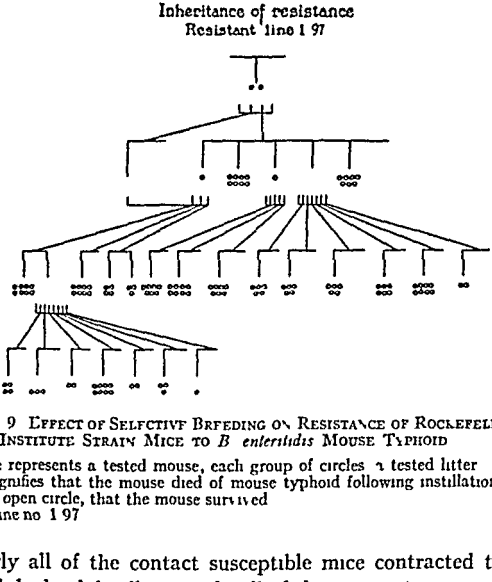


TEXT-FIG 8 EFFECT OF SELECTIVE BREEDING ON RESISTANCE OF ROCKEFELLER INSTITUTE STRAIN MICE TO *B enteritidis* MOUSE TYPHOID

Each circle represents a tested mouse, each group of circles, a tested litter A solid black circle signifies that the mouse died of mouse typhoid following instillation of the organisms, an open circle, that the mouse survived
Susceptible line no 244-1

found dead for mouse typhoid organisms, and by housing the progeny of susceptible and resistant lines together in the same cage for four weeks The stock has remained free from all infection Thus far, five lines of susceptible mice and six lines of resistant mice have been selected The susceptible lines show approximately 95 per cent mortality within fifteen days after exposure (text-fig 8), the control group shows 35 to 40 per cent, and the resistant lines show approxi-

mately 5 per cent mortality over the sixty-day period of observation (text-fig 9) The same differences in resistance are still manifest when the resistant mice are given ten times the dose and the susceptible mice $\frac{1}{10}$ of the standard dose The crucial test of the resistance of these mice has been their response to exposure to spontaneous infection Cages were arranged to contain 5 unselected mice given five million *B enteritidis* by mouth, together with 5 normal mice from the susceptible lines and 5 from the resistant lines In each instance,

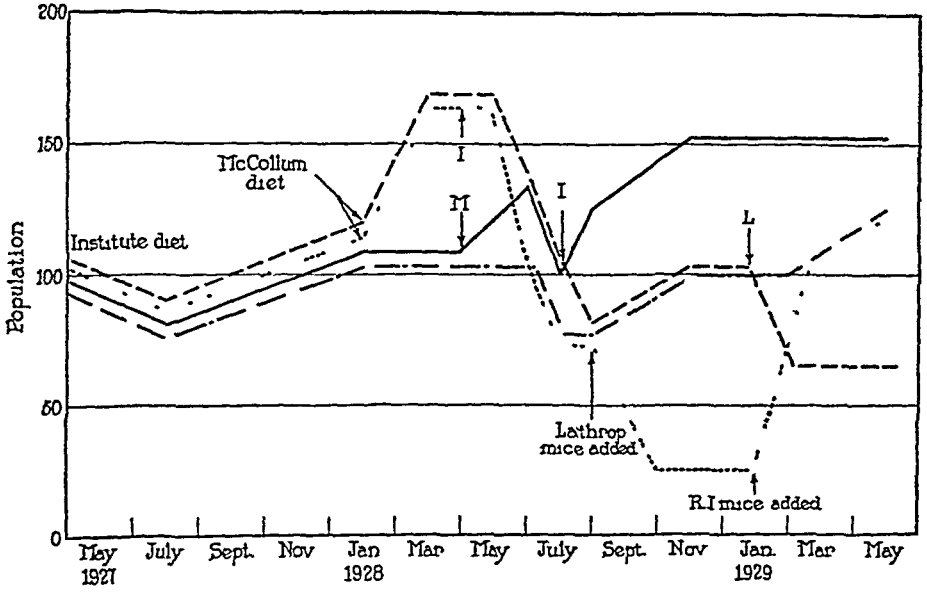


TEXT FIG 9 EFFECT OF SELECTIVE BREEDING ON RESISTANCE OF ROCKEFELLER INSTITUTE STRAIN MICE TO *B enteritidis* MOUSE TYPHOID

Each circle represents a tested mouse, each group of circles a tested litter A solid black circle signifies that the mouse died of mouse typhoid following instillation of the organisms, an open circle, that the mouse survived
Resistant line no 1 97

all or nearly all of the contact susceptible mice contracted the infection and died, while all or nearly all of the resistant mice survived and remained healthy Finally, it should be said that the resistant lines prove more refractory than the susceptible lines to fowl Pasteurella and pneumococci instilled intranasally These results prove that of 500 individuals selected at random, some possess a greater and some a less amount of resistance which is transmitted quantitatively to their progeny

Non-specific components of resistance, besides being inherited, are affected by environmental factors such as season and diet Thus, each month over a period of years, batches of 50 to 100 mice have been given mouse typhoid or Friedlander organisms with the result that mortalities, although irregular, have been definitely greater during the winter than the summer seasons (33) Again, mice raised on various adequate diets differ markedly in resistance One diet containing bread and milk has sufficed to raise the Rockefeller Insti-



TEXT-FIG 10 EFFECT OF CHANGING HOST RESISTANCE ON THE SPREAD OF *B enteritidis* MOUSE TYPHOID INFECTION IN MOUSE POPULATIONS HOUSED IN SINGLE CAGES

The chart pictures events in 4 populations for 2 years in terms of census figures

tute stock for more than fifteen years The fertility, duration of life, weight, appearance, and general health of these animals are excellent and have become standard Another diet used by McCollum has proved adequate for his rodent stock, and a third, a modified Steenbock ration, has likewise proved satisfactory And yet, mice of the same strain, raised on the bread and milk diet, are far more susceptible to *enteritidis* and *aertrycke* mouse typhoid, botulinus toxin, and mercury bichloride poisoning than mice fed on McCollum or Steenbock formulae No intensive efforts have been made thus far to

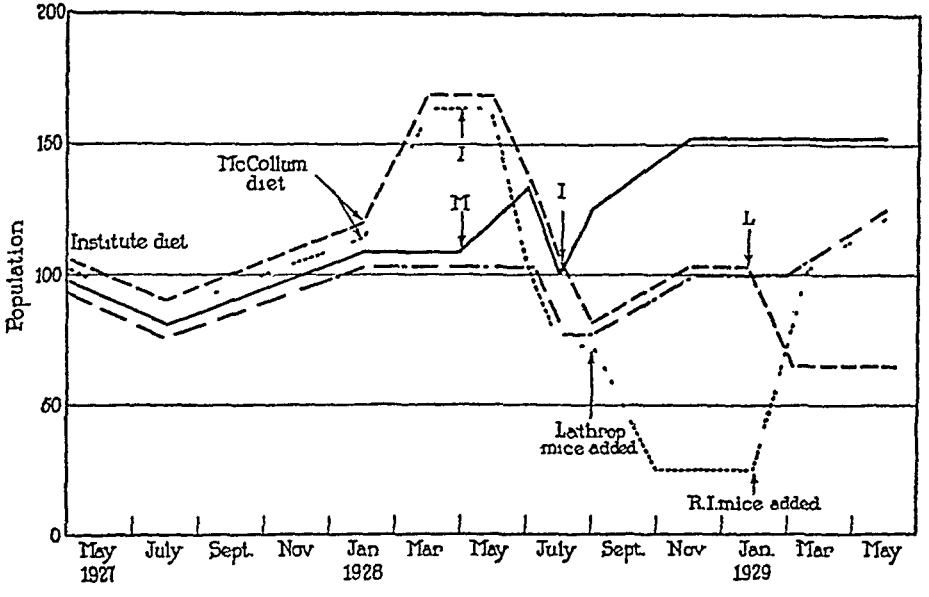
analyze these differences beyond demonstrating that butter fat a cod liver oil added to the bread and milk changed the "susceptib into a relatively "resistant" diet (34) Environmental factors, otl than those tested, such as exercise, fatigue, and exposure probal exert some influence on the resistance mechanism of the host, but yet have not been submitted to adequate examination

The known specific components of resistance appear to be acquir as a result of contact with the specific agent Just how potent th specific components may be and how important epidemiologically h not been determined Perhaps the most complete test of the questions has been reported by Topley and Greenwood (35) Anim were vaccinated with killed cultures of *B aertrycke* and exposed infection by being placed in an infected population The amount protection conferred was claimed to be significant only when a certa type of flagellar vaccine was employed, and then only when the e posure was mild and of brief duration The protection was not permanent one, it was noted during a period of about ten to thir days after exposure

In sum, the analyses of host resistance to infection have shown th individual animals exhibit definite amounts of non-specific inherit resistance to primary infection which take the form of a frequen distribution characteristic of the breed or race Moreover, this r sistance may be added to or reduced by such environmental influenc as season and diet, and may be supplemented by specific immuni components acquired as a result of contact with the specific microb agent

The effect of the resistance factor on the spread of infection h proved to be important In the first place, it was demonstrat that the form of explosive epidemic curves, that is the time distrib tion of morbidity or mortality, is an expression of individual differenc in the resistance of population constituents to a fixed dose of organisr of known virulence As shown previously, when a number of mi are each given an equal number of bacteria of a single culture, or even like dose of $HgCl_2$, they succumb after varying periods which wh plotted take the form of an epidemic curve similar to that of spont neously occurring epidemics (text-fig 3 and 4) In the case of tl experimentally treated mice, individual differences in resistance a

Non-specific components of resistance, besides being inherited, are affected by environmental factors such as season and diet Thus, each month over a period of years, batches of 50 to 100 mice have been given mouse typhoid or Friedlander organisms with the result that mortalities, although irregular, have been definitely greater during the winter than the summer seasons (33) Again, mice raised on various adequate diets differ markedly in resistance One diet containing bread and milk has sufficed to raise the Rockefeller Insti-



TEXT-FIG 10 EFFECT OF CHANGING HOST RESISTANCE ON THE SPREAD OF *B enteritidis* MOUSE TYPHOID INFECTION IN MOUSE POPULATIONS HOUSED IN SINGLE CAGES

The chart pictures events in 4 populations for 2 years in terms of census figures

tute stock for more than fifteen years The fertility, duration of life, weight, appearance, and general health of these animals are excellent and have become standard Another diet used by McCollum has proved adequate for his rodent stock, and a third, a modified Steenbock ration, has likewise proved satisfactory And yet, mice of the same strain, raised on the bread and milk diet, are far more susceptible to *enteritidis* and *aertrycke* mouse typhoid, botulinus toxin, and mercury bichloride poisoning than mice fed on McCollum or Steenbock formulae No intensive efforts have been made thus far to

analyze these differences beyond demonstrating that butter fat and cod liver oil added to the bread and milk changed the "susceptible" into a relatively "resistant" diet (34) Environmental factors, other than those tested, such as exercise, fatigue, and exposure probably exert some influence on the resistance mechanism of the host, but as yet have not been submitted to adequate examination

The known specific components of resistance appear to be acquired as a result of contact with the specific agent Just how potent these specific components may be and how important epidemiologically has not been determined Perhaps the most complete test of these questions has been reported by Topley and Greenwood (35) Animals were vaccinated with killed cultures of *B acertrycke* and exposed to infection by being placed in an infected population The amount of protection conferred was claimed to be significant only when a certain type of flagellar vaccine was employed, and then only when the exposure was mild and of brief duration The protection was not a permanent one, it was noted during a period of about ten to thirty days after exposure

In sum, the analyses of host resistance to infection have shown that individual animals exhibit definite amounts of non specific inherited resistance to primary infection which take the form of a frequency distribution characteristic of the breed or race Moreover, this resistance may be added to or reduced by such environmental influences as season and diet, and may be supplemented by specific immunity components acquired as a result of contact with the specific microbic agent

The effect of the resistance factor on the spread of infection has proved to be important In the first place, it was demonstrated that the form of explosive epidemic curves, that is the time distribution of morbidity or mortality, is an expression of individual differences in the resistance of population constituents to a fixed dose of organisms of known virulence As shown previously, when a number of mice are each given an equal number of bacteria of a single culture, or even a like dose of $HgCl_2$, they succumb after varying periods which when plotted take the form of an epidemic curve similar to that of spontaneously occurring epidemics (text-fig 3 and 4) In the case of the experimentally treated mice, individual differences in resistance are

the only variables which can account for the time distribution of mortality, and in the case of spontaneous epidemics the same is probably true

A second effect of the resistance factor is to control to a great extent the prevalence of endemic infection This relation, together with that of virulence and dosage, in actually inciting epidemics has been determined most effectively in studies of experimentally controlled epidemics of fowl (18), rabbit (26), and mouse Pasteurella (36) and mouse Friedlander (4) and *enteritidis* infections (9) These studies, in furnishing critical evidence on the questions at issue, may be regarded as typical of experimental epidemiology The results with the mouse populations exemplifying the findings as a whole will alone be considered

Mice constituting a population were assembled in a single large cage and maintained on the routine diet of bread and milk Two normal mice with identification marks were added daily A census was taken each day and the animals found dead were removed, autopsied, and cultured for the presence of the specific organism

The first experiment made was designed to test the mode of spread of Pasteurella in communities previously unexposed to these organisms (36) Populations 1, 3, and 4 received rabbit strains, Population 2 a fowl strain The three rabbit strains infected a few of the mice and died out at once, the fowl strain behaved in quite a different manner Eight of the 10 mice originally fed died within two weeks with Pasteurella septicaemia, after which no further deaths from this infection occurred for six weeks At that time, however, one of the immigrants succumbed Three weeks later, when the population numbered 61 individuals, an explosive epidemic of Pasteurellosis broke out, fatal to 77 per cent of the population in five days The epidemic then ceased abruptly and Pasteurella disappeared from the community The virulence of six strains obtained during the epidemic proved to be uniform and similar to that of the culture originally introduced into the community

The next experiments dealt with explosive and highly fatal epidemics of Friedlander pneumonia which arose spontaneously in the mouse populations (4) In the communities to which daily immigrations of 2 mice were continued, characteristic secondary waves

ensued These waves appeared when the population number reached a certain level They lasted a relatively similar number of days and reduced the population to a similar low number Subsequently, endemic periods intervened, followed by the disappearance of the disease in the late winter During the next summer, epidemics broke out again similar in each population but more protracted than the previous ones Fewer secondary waves ensued and the disease disappeared sooner The virulence of the Friedlander organisms, as determined by their ability to spread and incite typical epidemics in populations of previously unexposed mice, and by titrations of strains obtained during pre-epidemic, epidemic, post-epidemic, and interepidemic phases of the infection, proved to be constant The carrier rate increased prior to epidemic outbreaks and decreased shortly before the time of peak mortality A substitution of relatively susceptible for standard immigrants in a given population was followed by an increase in severity and frequency of the epidemics, while on the other hand, substitution of resistant for susceptible immigrants was followed by a decrease in the severity of the infection

The final experiments were made with *enteritidis* mouse typhoid in the same mouse populations (9) The infection took the form of periods of low grade mortality, interspersed with epidemiform outbreaks The daily deaths in the one case were either relatively constant or rhythmic in nine day intervals, the sudden increases in mortality were invariably associated with some definite environmental disturbance Cultures of the organisms taken from healthy carrier or mice dead of typhoid during pre-epidemic, epidemic, or inter epidemic phases of infection were of uniform pathogenicity Furthermore, the bacterial dissociation and bacteriophage phenomena, although abundantly present, seemed to play no part in determining the spread of infection The dosage of the organisms available to the population increased just prior to an increase in death rate and decreased in like manner before a fall in death rate Most important were the experiments made to test the effect on the prevalence of infection of changing population resistance Increasing population resistance by substituting an optimum for a barely adequate diet or by substituting relatively resistant for susceptible immigrants each day inaugurated periods of relatively low death rate, on the other hand, a depression of popula-

tion resistance by substituting the barely adequate diet for the optimum one, or susceptible for resistant immigrants, was followed by severe epidemic outbreaks

This concludes the present findings in experimental epidemiology It has been noted that various phenomena of population infection can be reproduced experimentally merely by the bringing together of host and microbic factors under suitable conditions In these infections, spontaneous or experimentally induced, strains of microorganisms from different populations differed occasionally in virulence—the more virulent being the less vegetative—but the effective virulence of strains in any one community proved stable during the entire endemic and epidemic periods of observation The dosage and host resistance factors, on the contrary, varied significantly with the amount and severity of infection Expressing these relationships in terms of cause and effect, it appears that the severity of infections in these animal populations was regulated by stable virulence and varying dosage and resistance factors In instances in which a foreign microorganism gained access to a hitherto unexposed population, the inherent virulence, the available dosage, and the amount and distribution of non-specific population resistance together determined the extent and severity of the infection In instances in which a microorganism was already present in the population, variations in population resistance and in available dosage were chiefly responsible for endemic and epidemic prevalences Fluctuations in population resistance were brought about by immigration, season, and diet acting upon the non-specific components, and by the infecting agent stimulating the specific components of resistance Fluctuations in available dosage resulted from variations in the host resistance and vector factors

To what extent is this experimental knowledge consistent with the known facts of human epidemiology? Briefly, there is evidence that the factors related to microbe and host suffice to account for the usual manifestations of cholera, typhoid, and the insect and animal-borne infections There are no data indicating that these factors do not suffice in other human infections Concerning the operation of these factors, there are grounds supporting the view that infections transmitted by vectors or contracted from foreign hosts, and infections

transmitted by water, milk, or food are for the most part controlled by a fluctuating dosage factor operating on a population of fluctuating resistance These diseases, taken together and considered from the time-space viewpoint, constitute the great majority of the total number Added to them are the parasitic and skin infections, the prevalence of which appears likewise to be controlled by the host and dosage factors The remaining group, that of respiratory diseases transmitted by direct contact, relatively very small but frequent in temperate climates, and therefore of great interest, are at present not as well understood One can only say that the available data do not contradict the view that their prevalence is controlled by fluctuations in the dosage of and resistance to specific agents of relatively fixed virulence

Further knowledge of the spread of human infections is now being sought by analyses similar to those utilized in experimental epidemiology Opie's studies on the spread of tuberculosis in families (37), Paul's observations of families with rheumatic disease (38), the work on the spread of upper respiratory tract pathogens among small groups of individuals (39), and detailed bacteriological, clinical, and sociological investigations of circumscribed communities, throw light on the manner and extent of dissemination of the specific agents and the relation of variations in dissemination, that is, in dosage, to variations in amount and severity of the infection in these communities They promise to make more clear the rôle of resistance in disease and the relative importance of its non-specific and specific factors

To broaden the scope of experimental epidemiology the studies must be extended from the acute, highly fatal bacterial diseases of animals to the more chronic ones and to virus infections This last step is already being taken (40) Knowledge of many types of infection in many species of hosts will be required for the proper development of epidemiology as a science

REFERENCES

(1) Topley, W W C *Lancet*, 1919, 2, 1
(2) Flexner, S, and Amoss, H L *J Exp Med*, 1922, 36, 9
(3) Amoss, H L *J Exp Med*, 1922, 36, 25
(4) Webster, L T *J Exp Med*, 1930, 52, 909
(5) Amoss, H L *J Exp Med*, 1922, 36, 45

(6) WEBSTER, L T *J Exp Med*, 1923, 37, 269
(7) WEBSTER, L T *J Exp Med*, 1928, 47, 685
(8) GREENWOOD, M, AND TOPLEY, W W C *J Hyg*, 1925, 24, 45
(9) WEBSTER, L T *J Exp Med*, 1930, 52, 931
(10) TOPLEY, W W C *J Hyg*, 1921, 19, 103
(11) WEBSTER, L T *J Exp Med*, 1924, 39, 129
(12) WEBSTER, L T *J Exp Med*, 1923, 37, 231
(13) WEBSTER, L T, HUGHES, T P, PRITCHETT, I W, AND BEAUDETTE, F R *J Exp Med*, 1930, 51, 219–274
(14) WEBSTER, L T *J Exp Med*, 1927, 45, 529
(15) WEBSTER, L T, AND BURN, C *J Exp Med*, 1927, 45, 911
(16) FREUND, R *Z Hyg u Infektionskrankh*, 1926, 106, 627
(17) SMITH, T, AND NELSON, J B *J Exp Med*, 1927, 45, 353, 365
(18) PRITCHETT, I W, AND HUGHES, T P *J Exp Med*, 1932, 55, 71
(19) WEBSTER, L T *J Exp Med*, 1926, 43, 573
(20) DE KRUIF, P H *J Exp Med*, 1921, 33, 773, 1922, 35, 561, WEBSTER, L T *J Exp Med*, 1925, 41, 571
(21) DE KRUIF, P H *J Exp Med*, 1922, 36, 309, WEBSTER, L T *J Exp Med*, 1926, 43, 573
(22) WEBSTER, L T *J Exp Med*, 1927, 45, 529, SMITH, D T *J Exp Med*, 1927, 45, 553, WEBSTER, L T, AND BURN, C G *J Exp Med*, 1927, 45, 911
(23) WEBSTER, L T, AND BURN, C G *J Exp Med*, 1927, 46, 855
(24) WEBSTER, L T, AND BURN, C G *J Exp Med*, 1927, 46, 887
(25) WEBSTER, L T *J Exp Med*, 1923, 37, 781, 38, 33, 45
(26) WEBSTER, L T, AND BURN, C G *J Exp Med*, 1926, 44, 359
(27) HUGHES, T P *J Exp Med*, 1930, 51, 225
(28) PRITCHETT, I W *J Exp Med*, 1925, 41, 195, 1926, 43, 161
(29) WEBSTER, L T *J Exp Med*, 1923, 38, 45
(30) WEBSTER, L T *J Exp Med*, 1926, 43, 555
(31) NEUFELD, F, AND ETINGER-TULCZYNSKA, G *Zt Hyg u Infektionskrankh*, 1931, 112, 492, 1931, 112, 754, 1932, 113, 482
(32) WEBSTER, L T *J Exp Med*, 1924, 39, 879, 1925, 42, 1
(33) PRITCHETT, I W *J Exp Med*, 1925, 41, 209, 1926, 43, 173
(34) WEBSTER, L T, AND PRITCHETT, I W *J Exp Med*, 1924, 40, 397, 1927, 46, 557
(35) GREENWOOD, M, TOPLEY, W W C, AND WILSON, J *J Hyg*, 1931, 31, 257
(36) WEBSTER, L T *J Exp Med*, 1930, 52, 901
(37) OPIE, E L Pathogenesis and Transmission of Tuberculosis Harvey Lectures, 1928–29
(38) PAUL, J R, AND SALINGER, R *J Clin Invest*, 1931, 10, 33, 53
(39) WEBSTER, L T, HUGHES, T P, AND CLOW, A *J Exp Med*, 1931, 53, 535, 1932, 55, 445
(40) GREENWOOD, M *Brit Med J*, 1931, 2, 231

FACTORS CONCERNED IN THE EVACUATION OF THE GALL BLADDER[1] [2]

ANDREW C IVY

Nathan Smith Davis Professor of Physiology and Pharmacology, Northwestern University Medical School, Chicago

Of all the hollow viscera, the gall bladder has been the most baffling in regard to the mechanism of evacuation In fact, a few investigators (1–4) have expressed the view that under normal conditions, the gall bladder does not evacuate its contents through the cystic duct However, most physiologists since the time of Haller have taught that the primary function of the gall bladder is to deliver concentrated bile to the duodenum at the beginning of digestion

Some of the difficulties which have been responsible for considerable disagreement in regard to the mechanisms concerned in the evacuation of the gall bladder are as follows (a) The gall bladder possesses but little smooth muscle when compared to such hollow viscera as the stomach, intestine, or urinary bladder,—a fact that has engendered considerable skepticism in regard to the contractile power of this organ (b) On direct mechanical or electrical stimulation, the gall bladder manifests relatively little or no evidence of contractility when observed under the conditions present during the usual laboratory and operating room procedures (c) In order to obtain evidence on the contraction processes in the gall bladder, considerable care and attention must be given to the depth of the anesthesia, blood pressure level, operative trauma, state of digestion, and method of registration of movements, in addition, technical skill and experience are required in certain phases of such a study (d) Because the gall bladder normally absorbs certain of the biliary constituents, notably water, and other substances introduced into its lumen, and may in the course

[1] The meaning of the term "evacuation of the gall bladder" is limited in this lecture to the exit of gall bladder contents via the cystic duct

[2] Lecture delivered before the Harvey Society, New York, February 18, 1932

of time under certain abnormal conditions (obstruction of the cystic duct) absorb most, if not all of the biliary constituents, one must consider the possibility that under normal conditions contents may leave the gall bladder only by being absorbed

The contractile power of the gall bladder Galen (5), in the second century, found from his dissections that the gall bladder is "sometimes very full, sometimes empty, and sometimes in an intermediate state," and taught that the gall bladder fills and empties like the other hollow viscera Haller (6) in 1755 taught on the basis of experimental evidence that the gall bladder contracts, but not to the extent of the urinary bladder, a fact that has been denied and reaffirmed by subsequent observers Doyon (7) in 1893 made the first graphic records of gall-bladder contractions Since then, such records have been obtained by every investigator who has used adequate methods Genuine contractions have been recorded from the gall bladder *in situ* in both anesthetized and unanesthetized animals, chiefly in the dog, and from "strips" of the gall-bladder wall

The motility of the gall bladder (8–14) in the dog is of two types first, a *tonic contraction* of the musculature which causes a prolonged increase in intra-gall-bladder pressure lasting from five to thirty minutes or more, and second, a *tonus rhythm* in which the gall bladder contracts and relaxes at a rate of from two to six times per minute In each type the musculature as a whole or a portion of it may contract With careful technique, a spontaneous tonus rhythm may be observed in 60 per cent of dogs or even in gall-bladder "strips" The tonic contraction may lead to a maximum rise in intra-gall-bladder pressure of from 20 to 30 cm of bile with the cystic duct obstructed (5 to 7 cc of bile being displaced from the gall bladder into pressure recording tubes) The changes in pressure produced by the tonus rhythm vary from 0 1 to 3 0 cm of bile At the height of the tonic contraction, the tonus rhythm usually disappears, and then reappears during the relaxation phase of the tonic contraction A sub-threshold stimulus for a tonic contraction may augment the rate and amplitude of the tonus rhythm without causing a general increase in tone A mild distension of the gall bladder may result in slight tonic contraction Prolonged mild distention usually causes a compensatory relaxation Ravdin (15) has recently observed rhythmic contractions of the gall

bladder of man *in situ* and in "strips" from the human gall bladder Some contractility of the gall bladder has been observed in every animal studied

Does the gall bladder evacuate? It is established and generally agreed that the gall bladder contracts, but opinion has not been unanimous as to whether the musculature prevents distention, facilitates absorption, or causes the expulsion of bile I suspect that it performs all three functions, since the smooth muscle of the intestine performs the same general functions However, before answering the question as to whether the gall bladder evacuates through a contraction of its musculature, it must be shown that it evacuates its contents through the cystic duct under normal conditions

Much indirect evidence (16) was reported during the period from 1885, when Heidenhain did his work on the secretion of bile, to 1924, when Graham and Cole visualized the gall bladder, which indicated that the gall bladder was the source of the dark, viscous bile that flowed from the common bile duct after certain procedures During the latter part of this period, the stimulating idea of Meltzer (17) of the reciprocal relation of the gall bladder and the sphincter of the common duct was recorded *On this idea were based the provocative* observations on "non-surgical drainage of the gall bladder" of Lyon (18) Much credit is due to Meltzer and Lyon for re awakening the interest of the medical world in regard to gall-bladder physiology Probably the most direct attacks on the problem during this period were those of Auster and Crohn (19), Winkelstein (20) and others (21, 33a) who placed substances in the gall bladder to determine their time and mode of expulsion The discovery that the gall bladder can be visualized by tetraiodophenolphthalein by Graham and Cole (22) in 1924, gave us a new method for the study of gall-bladder physiology in animals and man The discovery of Boyden (23) that egg yolk will cause bile to disappear from the gall bladder of the cat, and by Sosman, Whitaker and Edson (24) that most fats have a marked effect on the disappearance of the cholecystographic shadow in man provided physiologists and clinicians with an important and a potent excitant of gall-bladder activity Shortly after these discoveries, Whitaker (25) showed that the cat s gall bladder filled with iodized oil is evacuated through the cystic duct after the oral administration of fatty

substances, McMaster and Elman (26) by the method of "altercursive intubation" demonstrated the expulsion of a portion of the gall-bladder contents by contraction of the viscus after feeding, and Higgins and Mann (27) under direct vision observed the gall bladder of guinea pigs and dogs to contract and evacuate through the cystic duct, a fact that has been confirmed for the guinea pig by Burget and Brocklehurst (28) and for the dog by Lueth, Ivy and Kloster (14), and by Ivy, Sacks and Drewyer (29) who have made moving pictures of the phenomenon So from direct evidence, it is established that the gall bladder of the cat, dog and guinea pig during contraction may evacuate its contents through the cystic duct

Evidence has been obtained by Halpert and Hanke (30) in the rabbit which indicates that the rabbit's gall bladder does not evacuate through the cystic duct, although using the same method they found that the dog's gall bladder evacuates completely (31) each day via the cystic duct We have been inclined to agree with their observations on rabbits, because on using the ordinary tambour and manometer technique, we have not been able to obtain definite contractions of the gall bladder of the rabbit (14) However, Dr Walsh and I (32) have demonstrated recently by direct observation and photography of the gall bladder and by chemical analysis of the duodenal contents that the gall bladder of the rabbit may evacuate under the stimulation of "cholecystokinin," from 60 to 80 per cent emptying being obtained The contractions were pseudo-peristaltic in nature, usually starting at the neck as Higgins (33) described in the bullhead (fish), although the contractions might start at both ends and meet in the middle or start in the middle and move towards both ends Evacuation occurs either with an intact common-duct sphincter or with the common duct cannulated and the hepatic ducts tied We could not obtain rapid evacuation of iodized oil in the rabbit, the shadow disappeared gradually but not completely throughout an observation period of five days We did observe marked changes in contour of the gall bladder analogous to those observed under direct vision and photography. Evidently the iodized oil was too viscous to be evacuated by the relatively feeble contractions of the rabbit's gall bladder Babkin and Webster (33a) have observed evacuation of the rabbit's gall bladder after egg yolk and cream were given by stomach tube

:quivocal evidence that the gall bladder of man may evacuate
e cystic duct is also available This evidence is of three kinds,
al, chemical and roentgenological
ir surgeons have reported that they have seen the gall bladder
r on duodenal stimulation in patients with the abdomen open
(34) of Nebraska reported one case with the abdomen open in
a distended gall bladder started to collapse five minutes after
ing magnesium sulphate (50 cc , 33 per cent) into the duodenum
)parent contraction was not seen Pribram (35) of Austria re-
l a case in which the gall bladder emptied after instillation of a
ne solution (20 cc , 10 per cent), active contraction being ob-
l Matsuo (36) of Japan exposed the gall bladder under panta-
:opolamine and local anesthesia in two patients In one case
stillation of magnesium sulphate into the duodenum was effective
.cuating three-fourths of the gall bladder contents within thirty-
inutes Then the vesicle was partially filled with azorubin S,
which magnesium sulphate was again instilled and the dye
ied from the duodenal drainage The gall bladder was seen to
ict The dye test was repeated on the second case with the same
s except that the gall bladder was not seen to contract Trom-
nd Hempel (37) have reported five cases in which India ink was
l in the gall bladder at operation and then obtained from the
nal drainage after instilling 60 per cent glucose into the duodenum
did not look for evidence of contraction
emical evidence bearing on the question of whether the human
ladder evacuates has been obtained by analysing the duodenal
nts for iodine, bile pigment, and cholesterol before and after the
ation of magnesium sulphate, N/20 HCl, and oleic acid solutions
the duodenum In the experiments in which an analysis for
: concentration was made, the gall bladder was previously
lized with tetraiodophenolphthalein In such experiments per-
:d by Lake (38) and by Lyon (18), the results indicate that
all bladder evacuated a considerable portion of its high iodine-
aining bile Mann and Higgins (27) obtained similar results in
og However, Sweet (1) has interpreted these results as indicat-
ie duodenal stimulation caused the iodine to be absorbed rapidly
ie gall bladder mucosa and then re excreted by the liver from

whence it passed into the duodenum Such a view is hardly tenable on the basis of the rapid change in the gall-bladder shadow that so frequently occurs after the ingestion of egg yolk and fat, and in view of the slow rate of absorption of tetraiodophenolphthalein by the gall bladder as observed in the experiments of Sweet (1) (39a) and Johnson (39), and in view of the fact that some normal subjects show very little change in the gall-bladder shadow on starvation or on eating several carbohydrate meals within twenty-four hours (24) (49) (41) Of course, it is possible that duodenal stimulation with fat increases the rate of gall-bladder absorption, but Johnson (39) reports that a fat meal does not increase the rate of absorption of the dye

Adlersberg and Taubenhaus (42), using the Meltzer-Lyon method, have reported a three to ten-fold increase in bilirubin concentration of the duodenal contents after the instillation of magnesium sulphate This has been confirmed by Jones and Walsh (43) in my laboratory for normal subjects, they found cholesterol also to be present in some samples of duodenal contents in the concentration in which it is present in gall-bladder bile, and since absorption by the "normal epithelium" of the bile ducts does not occur according to all available evidence, the only known source of such bile is the gall bladder

The cholecystographic evidence that the human gall bladder evacuates is now conclusive (23) (44) Much cholecystographic evidence has been obtained by Boyden and others (41) (24) (45) from human subjects showing marked changes in the contour and size of the gall bladder within ten or fifteen minutes (against gravity, subject standing) after the application of various procedures which are known to cause the gall bladder of animals to contract and evacuate In order to account for some of these changes on the basis of the absorption of dye, absorption would have to occur in the gall bladder more rapidly than it occurs in a loop of intestine of equal size The most striking evidence, however, is that by using the proper radiographic technique, the cystic and common bile ducts become visualized after giving a fat meal to subjects with a normal cholecystogram Boyden (44) and Pendergrass (46) have made such observations I have seen numerous such films as shown in figures 1, A, B, and C, in the department of Dr. James T Case, who states that either the cystic duct, common duct, or a portion of the hepatic duct, or all, become visible after the

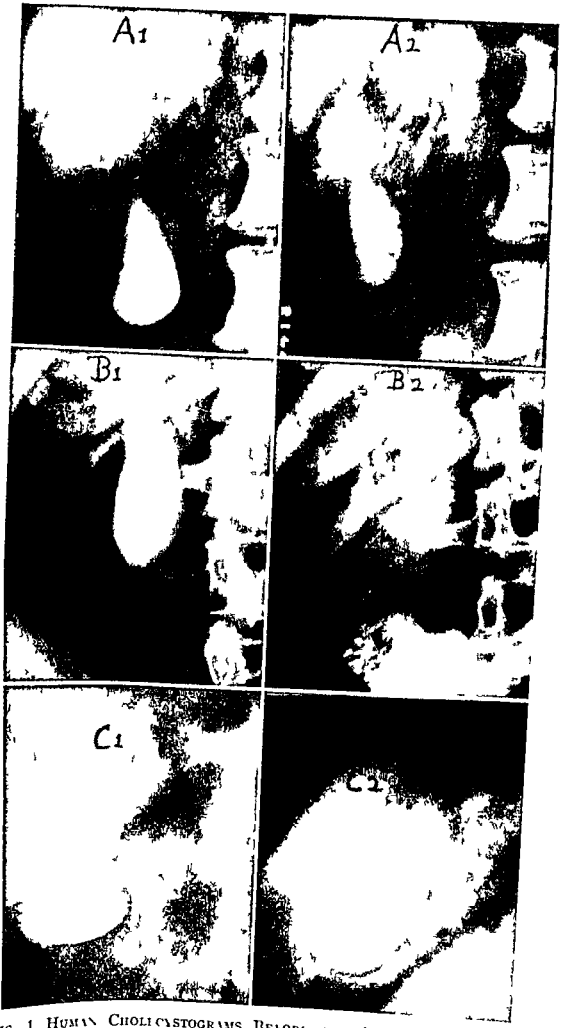


FIG 1 HUMAN CHOLECYSTOGRAMS BEFORE AND AFTER A FAT MEAL

The pictures A B and C were taken fourteen hours after the intravenous injection of the dye Then a fat meal was ingested and the pictures A B and C were taken 20 min later In A and B note cystic and common ducts In C note cystic, common and hepatic ducts

fat meal in about 10 per cent of patients with a normal cholecystogram The ducts may become visible within 15 or 20 minutes after egg yolk Such roentgenograms cannot be explained on the basis of absorption of the dye from the gall bladder and re-excretion by the liver If so, the hepatic ducts should be as visible as the common and cystic ducts and in those cases in which the hepatic ducts become visible after the ingestion of egg yolk and cream, there should not be a clear cut line of demarcation between visibility and invisibility, as is seen in figure 1, C_2 This and the foregoing evidence conclusively demonstrate that the gall bladder of man evacuates under normal conditions via the cystic duct

Since the gall bladder of the cat, dog and man while contracting may evacuate via the cystic duct, the obvious deduction is that its musculature plays an important rôle in the evacuation process The pressure exerted on the contents of the gall bladder during a maximal contraction has not been measured in man, in the dog a maximal pressure of from 20 to 30 cm of bile is exerted,—a pressure that is not to be considered as trivial However, before one can be assured of the sufficiency of the above deduction, one must consider (a) the mechanisms concerned in the activation of the gall bladder musculature, and (b) the possibility that evacuation through the cystic duct may be due in part to other factors than contraction of the gall-bladder musculature

Mechanisms concerned in gall-bladder contraction The following causal mechanisms for gall-bladder contraction have been suggested (1) local stimulation by distention or by "pungent" bile, (2) nervous reflex stimulation from various portions of the gastro-intestinal tract, (3) long nervous reflexes from the higher brain centers and, (4) humoral agents, including the hormone, cholecystokinin As is true for other hollow viscera, all may be concerned

Local stimulation It is interesting that Galen (5) states, "For since it was shown that the gall bladder attracts its own special juice so as to be often found full, and that it discharges it soon after, this desire to discharge must be either due to the fact that it is burdened by the quantity or that bile has changed in quality to pungent and acrid " No direct experiments have been done on the possibility that the gall bladder may be caused to discharge its contents in response

to an adequate tension stimulus or irritation of the mucosa by the contents The facts that the gall-bladder wall contains ganglia, that spontaneous contraction or evacuation has been observed, that distention of the isolated viscus will cause a slight contraction, and that a certain optimum distention and pressure are required for a maximum response to a stimulus, indicate that local stimulation of the gall-bladder wall may be a factor I should be surprised if this were not true There is indirect evidence to the contrary, however This topic deserves further investigation

Nervous reflex stimulation from various portions of the gastro-intestinal tract Since the various portions of the gastro intestinal tract may be reflexly inhibited or excited by stimulation of distant parts, the same might be expected to be true of the gall bladder Boyden and Birch (47) have obtained evidence showing that electrical excitation of the pyloric antrum frequently induces a slight contraction, and that the electrical excitation of the intestine and particularly the cecum induces relaxation of the gall bladder That the gall bladder may be inhibited reflexly is of obvious clinical significance But there are no good experimental or clinical data bearing on the problem of a relation between gall bladder emptying and enteritis, colitis or constipation

Meltzer's theory (17) that a reciprocal innervation exists between the gall bladder and the common duct sphincter is sound physiologic philosophy According to this theory gall-bladder contraction reflexly causes relaxation of the sphincter—not the reverse In spite of the fact that there is much evidence pro and con, the evidence most free from technical objections (48) (49) shows that when the gall bladder contracts forcibly, the resistance to the flow of bile into the duodenum decreases However, it is known that the gall bladder may contract against a contracted "sphincter" (13) (23) There is no crucial evidence at hand proving the theory One is not surprised at the disagreement in the literature in view of the multiplicity of factors, the slight pressure changes observed, and the variation in response of the sphincter and gall bladder from time to time in the same animal There is even disagreement in regard to the reciprocal relation of the stomach to its sphincters, which is best explained by the observations of Carlson and Litt (50) that the muscular response

obtained frequently depends on the physiological state of the neuromuscular mechanism at the time the stimulus is applied That the mechanism of reciprocal innervation is not essential for gall-bladder evacuation is shown by much crucial evidence to be cited later

Long nervous reflexes from higher brain centers Although a number of investigators (7) (8) (9) (12) have obtained motor effects in the gall bladder on excitation of the vagi and splanchnic nerves, none has claimed that the changes are marked Appreciable emptying has not been obtained by vagal stimulation in unanesthetized dogs (25) (40) Some (26) (49) (52) have observed what might be termed a "psychic" contraction of the gall bladder with the expulsion of from 1 to 3 cc of bile on the sight or taste of food or the aroma of bacon Some report failures (51) (53) (40) Crandall (40) has shown that "sham feeding" of egg yolk and meat for from one-half to one hour in the dog, the gastric juice being removed, does not cause an apparent change in the size and density of the gall bladder visualized with tetraiodophenolphthalein This does not mean that a "psychic" contraction of the gall bladder does not occur, especially in view of the well known quantitative variation of "psychic" secretion of gastric juice in man and dog The disagreement only indicates that the response is slight and variable

Humoral agents Two different types of humoral agents (54) are known to be concerned in causing gastric secretion secretagogues, which are present in food or arise from the digestion of food and act both locally and by being absorbed into the blood, and a hormone, histamine-like in nature, which has a specific effect on the gastric glands By analogy, it is possible that the gall bladder may be caused to contract following the ingestion of a fatty or protein meal, either by the absorbed fatty substances, or by a hormone produced by the action of fatty substances or acid chyme on the gastro-intestinal mucosa

This possibility occurred to a number of investigators at about the same time, particularly Boyden (23), Whitaker (25), Copher and Illingworth (55) and others (11), because Whitaker had obtained contraction and evacuation of the "denervated" gall bladder and McMaster and Elman had made a similar observation with the cystic duct cut and intubated Boyden tried blood transfusion with sugges-

tive results Whitaker, and Copher and Illingworth and others (20) (11) tried "secretin" with negative results, Braga and Campos (64) and Brugsch and Horsters (65) obtained positive results Whitaker injected emulsified olive oil intravenously with positive results, but since emulsified liquid petrolatum (56) produced the same effect, he questioned the physiologic nature of the response Higgins and Wilhelmj (57) obtained no evacuation on injecting various emulsified fats intravenously, and Silverman and Dennis (58) observed evacuation in man without a significant change in blood fat We have found that egg yolk intravenously does not cause gall-bladder contraction Emulsified olive oil causes an increase in gall-bladder pressure which is an artifact due to marked splanchnic congestion Chyle has been injected with negative results, and Boyden has obtained evacuation after a fat meal with the thoracic duct tied near the cysterna Hence, post-absorptive circulating fatty substances appear not to be responsible for gall-bladder contraction and evacuation

Hormone mechanism In 1926, being impressed by the observations just mentioned, Dysart and I were successful in transplanting the gall bladder into the omentum, but could not obtain a contraction from the transplant, probably because it was imbedded in an omental mass

At that time we were engaged in an attempt to isolate the hormone "secretin" for the purpose of perfecting a human pancreatic function test It occurred to me that since fats are potent excitants of pancreatic secretion and since bile and pancreatic juice play such an important rôle in fat digestion, the hormone "secretin" might cause the gall bladder to contract Having a number of different "secretin preparations" on hand, Dr Oldberg and I undertook to assay them on the gall bladder of the cat, and found that some of them caused the vesicle to contract This was duplicated on the dog, on which animal most of our work has been done

The method used for recording changes in gall-bladder pressure is one well known to physiologists and is shown in figure 2 By cannulating the cystic duct aseptically under ether anesthesia and then permitting the animal to recover, changes in gall-bladder pressure were followed on unanesthetized animals It was found that solutions containing as little solid material as 3 mgm , on intravenous injection would cause from 1 0 to 11 5 cm rise in intra-gall-bladder pressure

which persisted from ten minutes to one hour. A series of injections would cause a step-like rise in pressure amounting finally to from 20 to 30 cm of bile, a pressure which is obtained in the dog after feeding egg yolk or fat (26) (27) Recently we have obtained definite responses with as little as 0 2 mgm of solid material, and slight changes with as little as 0 06 mgm Though we have injected many drugs

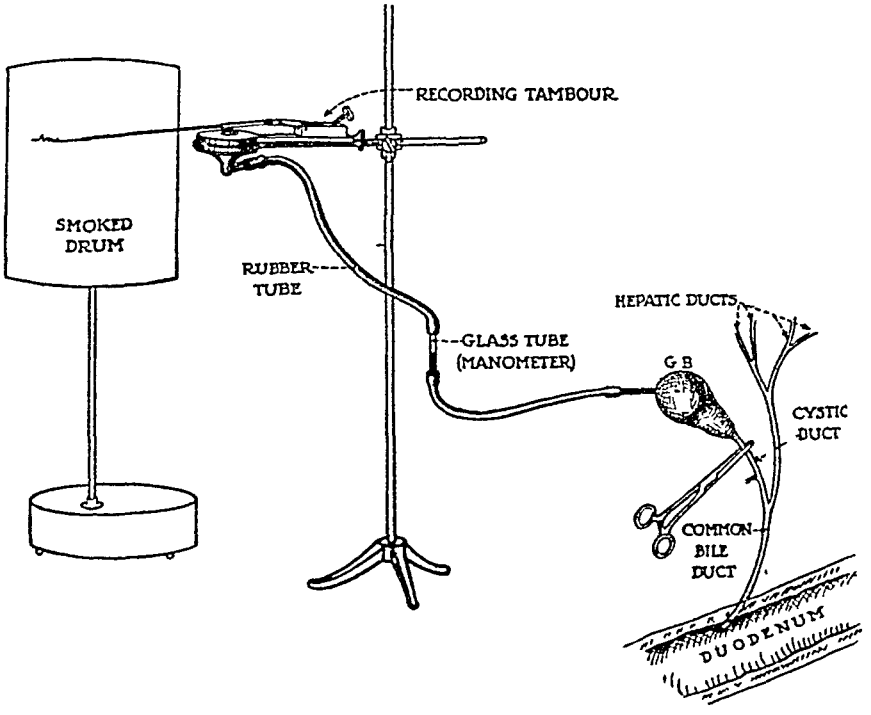


FIG 2 This figure shows the apparatus and method used for recording gall-bladder contractions The clamp on the cystic duct frequently occluded the cystic artery and some of the lymphatics Edema of the gall bladder did not occur As a rule better contractions following cholecystokinin were obtained when it was not necessary to occlude the cystic artery (Reprinted by permission of the Detroit Proceedings of the Inter State Post Graduate Medical Association of North America, October 21–25, 1929

and chemical substances, a response similar to that obtained with the highly "purified" acid extracts of upper intestinal mucosa has not been observed Acetyl choline (23) (59) and pilocarpine cause a gall-bladder contraction, but these substances affect blood pressure and are antagonized by atropine Relatively large doses of adrenalin intravenously, but not subcutaneously (23), may cause some contraction (41) The active principle of extracts of upper intestinal mucosa

is the most potent intravenous excitant of gall-bladder contraction known at present

It has been shown that the rise in intra-gall-bladder pressure caused by cholecystokinin is not due to extraneous factors such as increase in liver volume (fig 3), diaphragmatic changes, and gastric or intestinal motility (14) The gall bladder of the dog and rabbit has been seen by direct vision and photography to contract and evacuate after an injection

A large dose of atropine (2–10 mgm) decreases, but does not abolish the response Ergotamine (1 5 mgm) which *per se* causes a slight contraction of the gall bladder, does not decrease, but tends to in-

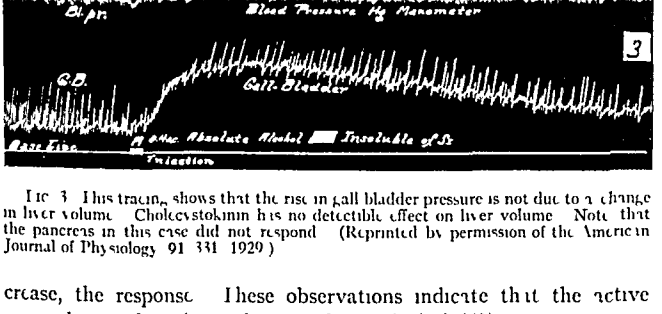


FIG 3 This tracing shows that the rise in gall bladder pressure is not due to a change in liver volume Cholecystokinin has no detectible effect on liver volume Note that the pancreas in this case did not respond (Reprinted by permission of the American Journal of Physiology 91 331 1929)

crease, the response These observations indicate that the active principle acts directly on the smooth muscle (14) (59)

The active principle in the doses employed had a variable effect on intestinal motility, sometimes increasing at other times decreasing or having no effect (14)

Since we have made preparations which caused gall-bladder contraction and not pancreatic secretion and vice versa, we believe that the gall bladder contracting principle is different from secretin (60) We have, therefore, proposed the term "cholecystokinin" to designate the gall-bladder contracting principle of extracts of the upper intestinal mucosa Cholecystokinin and secretin are closely related, and on occasion we have observed the apparent conversion of one into the

other But the question of identity will not be settled until one or the other or both have been crystallized

Two observers (62) (63) have reported contraction of gall-bladder "strips" or of the isolated organ on the introduction of "secretin" solutions into the bath One observer (61) failed Jung (66) has found that the isolated gall bladder of the guinea pig in a "bath" is very susceptible to change in pH However, when cholecystokinin is added, taking precautions not to disturb pH, a contraction results From five to ten intravenous dog doses must be added to the bath,

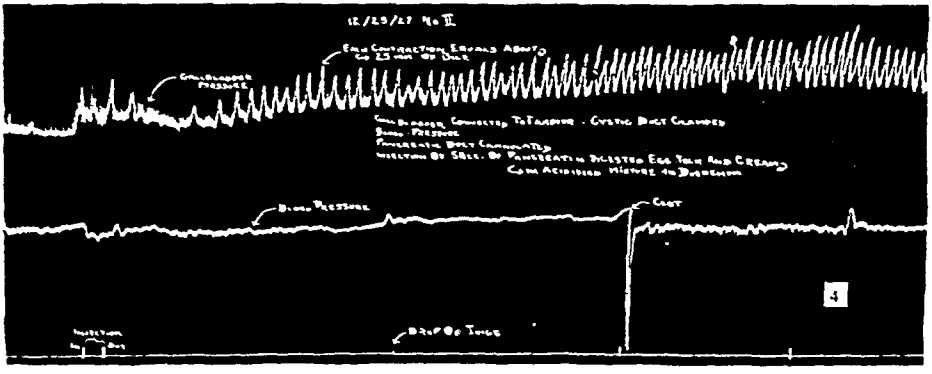


FIG 4 The upper tracing shows the change in gall-bladder pressure after the introduction of a slightly acidified pancreatic digest of egg yolk and cream into the duodenum A slowly increasing tonic contraction of the gall bladder as a whole is to be noted on which is superimposed a tonus rhythm augmented in rate and amplitude Each tonus rhythm exerted a pressure of 2 5 cm of bile on the contents, and they occurred at a frequency of from two to three per minute (Reprinted by permission of the American Journal of Physiology, 86 605 1928)

probably because cholecystokinin diffuses very slowly through the gall-bladder serosa

It has been found that when either hydrochloric acid of the strength that is found normally in the stomach or egg yolk, cream, and olive oil digested with pancreatin are introduced into the duodenum, a contraction of the gall bladder is induced (fig 4) The contraction begins in about two minutes Following the introduction of emulsified and partially digested fat, the gall bladder manifests a slow tonic contraction on which is superimposed an augmented tonus rhythm This, we believe, represents the normal type of gall-bladder response to ingested egg yolk and fat and is well calculated to expel contents from the gall bladder

The observation that the introduction of dilute HCl (N/10-N/20) into the duodenum caused the gall bladder to contract but that a reasonable intravenous injection of the acid did not, made it possible to test out a hormone hypothesis for gall-bladder contraction Accordingly cross circulation experiments were done using dogs with compatible bloods It was found that the introduction of acid into the duodenum of one dog caused the gall bladder of this dog to contract within two minutes and the gall bladder of the other in from eight to twelve minutes (13) The obvious interpretation of this

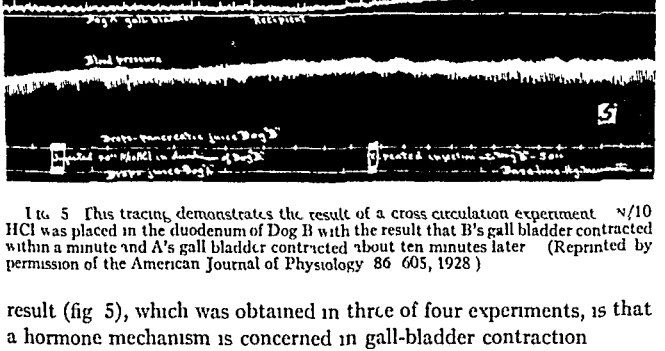


Fig 5 This tracing demonstrates the result of a cross circulation experiment N/10 HCl was placed in the duodenum of Dog B with the result that B's gall bladder contracted within a minute and A's gall bladder contracted about ten minutes later (Reprinted by permission of the American Journal of Physiology 86 605, 1928)

result (fig 5), which was obtained in three of four experiments, is that a hormone mechanism is concerned in gall-bladder contraction

Although no other excitant of cholecystokinin production than dilute hydrochloric acid was used in our cross circulation experiments, we do not believe that acid is the sole excitant Just as there are other excitants of secretin production than acid, there are probably other excitants of cholecystokinin production Acid was chosen for our experiments because it gave a rapid response and is a pure chemical substance We have shown that filling of the gall bladder occurs in gastrectomized dogs and evacuation is induced by feeding egg yolk Also, perfusion of egg yolk through the stomach in some dogs with a pouch of the entire stomach induces evacuation of the gall bladder (56) (67) Small quantities of cholecystokinin have been obtained from the pyloric mucosa (68)

Cholecystokinin injected intravenously has been observed to cause evacuation of iodized oil from the gall bladder of the dog, of normal gall-bladder contents in the dog, and rabbit, and to cause the Graham-Cole shadow of the gall bladder in dog (fig 6) and man (fig 7) to

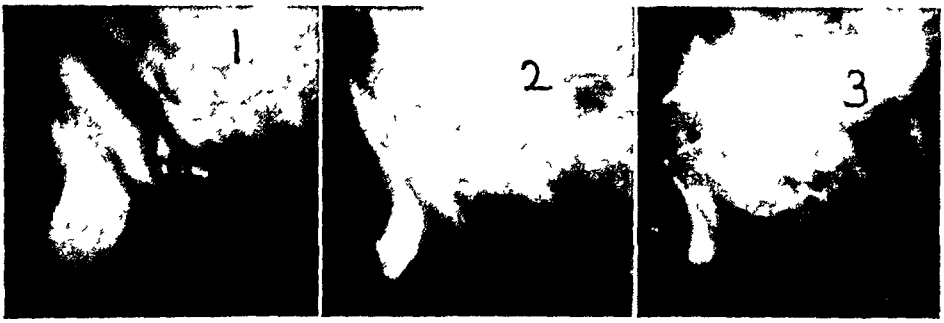


FIG 6 This figure demonstrates the evacuation of iodized oil from the gall bladder under the influence of cholecystokinin "1" is the control picture, "2" was taken at 30 minutes, and "3" at one hour Seven injections of cholecystokinin were made at 10-minute intervals In "3" note the injection of the hepatic duct of the right lower lobe of the liver (Reprinted by permission of the American Journal of Physiology, 86 605, 1928)

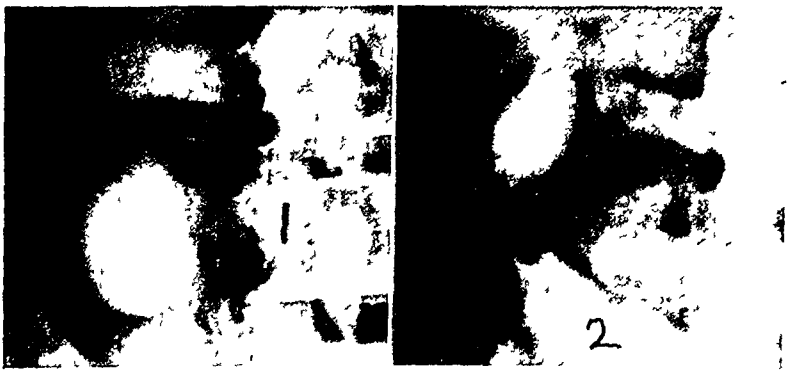


FIG 7 THE GALL BLADDER OF A PATIENT (MAN) BEFORE (1) AND AFTER (2) THE INJECTION OF THREE DOSES OF CHOLECYSTOKININ AT 10 MINUTE INTERVALS

The changes in the gall-bladder shadow become evident within five or ten minutes of the first injection The second picture was taken about 45 minutes after the first (Reprinted by permission of Endocrinology, 14 343, 1930)

disappear rapidly Cholecystokinin works more rapidly, but no more effectively than a meal of egg yolk, cream and olive oil This has been confirmed by Whitaker (59) The amount of evacuation obtained within one hour by successive injections of cholecystokinin varies from

animal to animal, just as occurs when a fat meal is ingested We have obtained from thirty to eighty per cent evacuation of iodized oil in one hour In man we have obtained 50 per cent reduction of the shadow in one-half hour after three injections of cholecystokinin (45)

On the basis of the evidence at hand it is held that a hormone mechanism is concerned in gall-bladder contraction and evacuation The hormone (cholecystokinin) is closely related to but probably not identical with secretin, and is formed by the upper intestinal mucosa when in contact with acids, and probably fatty and other substances that cause secretin formation

Spontaneous contraction Almost every recent investigator in this field has occasionally observed spontaneous contraction and evacuation of the gall bladder in the dog, the cat and man They have resulted under conditions that preclude a definite interpretation, and hence various interpretations have been offered, none of which is acceptable in fact

Factors other than contraction which may be concerned in evacuation via the cystic duct There are some investigators of gall-bladder physiology who are convinced that this organ evacuates through the cystic duct but maintain that evacuation is accomplished primarily by forces other than intrinsic contraction of the gall-bladder musculature This difference of opinion has led to the performance of numerous ingenious experiments by Winkelstein (20), McMaster and Elman (26), Whitaker (25), Burget (28) (69), Boyden (23), Mann, Potter and Higgins (27) (48) and Graham, Kodama, Copher and Illingworth (22) In regard to the source of the extrinsic forces, the following suggestions have been made (1) Increase in intra-abdominal pressure incident to inspiration with a relaxed common duct sphincter squeezes bile from the gall bladder into the duodenum (2) The filled stomach with gastric and duodenal peristalsis pushes the gall bladder against the liver and mechanically massages the bile from the gall bladder (3) The ebb and flow of bile with the elasticity of the gall bladder wall and a siphonage effect wash out and drain the bile from the vesicle (4) The milking action of duodenal peristalsis and changes in duodenal tone assisted by changes in intra-abdominal pressure and the elasticity and tone of the gall-bladder wall produce a passive evacuation of the organ (5) Peristalsis of the biliary ducts

in those animals (guinea pig, pigeon, bullhead fish) in which it occurs may play a rôle in emptying the gall bladder. On the basis of the evidence presented in support of these extrinsic forces, I believe there is an element of fact involved in each instance In order to evaluate these extrinsic factors, it is necessary, first, to determine if the gall bladder will evacuate in their absence, and second, if it does, how these extrinsic factors modify gall-bladder evacuation

It is definitely established that in the absence of extrinsic forces the intrinsic musculature of the gall bladder in the dog is sufficient to expel most of the contents from the vesicle McMaster and Elman (26) inserted a tube into the cystic duct, another into the upper end of the common duct, and a third into the lower end of the common duct. By connecting these tubes bile could flow from the liver into the gall bladder or into the duodenum In this manner the gall bladder was excluded from the flushing action of hepatic bile and the sucking action of duodenal peristalsis When the gall bladder was filled with bile, it was found that when the animal was fed, a considerable amount of bile was forced from the gall bladder against pressure (20 cm bile) This cannot be accounted for by an increase in intra-abdominal pressure since the amount of food ingested causes no increase in intra-abdominal pressure according to the experimental data of Cannon (70) and Kelling (71) Higgins and Mann (27) by inserting a tube in the common bile duct and tying the hepatic ducts with the abdomen open, observed evacuation of the gall bladder to occur on introducing a fat meal into the duodenum No bile left the gall bladder until the fat was introduced, even though the common-duct sphincter control had been removed Copher and Illingworth (55) filled the gall bladder with iodized oil and placed a cannula attached to a rubber balloon into the cystic duct Following an egg yolk meal the gall bladder emptied a considerable amount of the oil into the rubber bag

The rôle of intra-abdominal pressure as affected by deep respiration and vomiting in promoting evacuation of the gall bladder has been stressed by Winkelstein (20) He properly points out that the common-duct sphincter must be relaxed to observe the phenomenon It is true that deep respirations or vomiting may induce changes in intravesical pressure as high as 10 cm of bile pressure Normal respira-

tions, however, with or without the abdomen closed, rarely cause a fluctuation of more than 1 or 2 cm of bile pressure When the gall bladder is filled with iodized oil, a very viscous substance, vomiting or marked changes in intra-abdominal pressure artificially induced usually causes no evacuation (24, 25, 26, 55, 75) I have observed slight evacuation of the gall bladder during vomiting when the gall bladder is filled with iodized oil and the sphincter held open by a cannula Almost complete evacuation occurred after a fat meal According to some (20) (22), deep manual pressure in the upper right quadrant will squeeze some bile from the gall bladder, but others (24) have not observed this even after atropine The reason for the discrepancy probably lies in the tone of the common duct sphincter or duodenal musculature Hence, if respiration and normal changes in intra-abdominal pressure play a minor rôle, their effectiveness depends entirely on the common-duct sphincter

There is no clear cut evidence supporting the suggestion that the peristalsis of the stomach and duodenum during digestion mechanically massages the bile from the gall bladder (89) That this factor is not even likely is shown by numerous observations to the effect that a carbohydrate meal has little or no effect on the disappearance of the cholecystographic shadow in man

Graham and coworkers (22) (55) have stressed the possibility that the ebb and flow of fresh bile from the liver with the elastic recoil of the gall-bladder wall may exert a washing out effect Copher, Kodama and Graham (22) visualized the gall bladder and then tied the hepatic ducts in dogs A fat meal failed to cause disappearance of the shadow Scott and Whitaker (78), however, in a similar experiment in cats, obtained emptying of iodized oil (55) The only directly unchallenged experiment in support of this possibility is the following experiment The gall bladder was removed and a rubber bag was substituted Tetraiodophenolphthalein was administered and the rubber bag filled and visualized In five days the shadow had practically disappeared Whitaker (25) performed the same experiment using iodized oil instead of iodized bile and observed no emptying of the iodized oil after feeding The results of these experiments indicate that extrinsic forces such as the ebb and flow of bile and the sucking action of duodenal peristalsis or changes in the

common-duct sphincter are capable of very slowly evacuating iodized bile, but not the more viscous iodized oil Boyden (44) has shown that the gall bladder of man will empty against gravity It is interesting that at one time gravity was supposed to be a factor in emptying of the stomach (70) In view of the evidence cited above on the intrinsic ability of the gall bladder to evacuate, only a minor rôle may be ascribed to the washing out effect of the ebb and flow of bile

In any consideration of the motor activity of the gall bladder, serious attention must be given to the common-duct sphincter and duodenal motility All investigators agree that either the common-duct sphincter or duodenal activity or both play an important rôle in the filling of the gall bladder Most agree that they play some rôle in the evacuation process

I thought that duodenal peristalsis was the prime factor in gall-bladder evacuation until the experiments of McMaster and Elman and Higgins and Mann were published, and I doubted until recently the existence physiologically of a special common-duct sphincter This opinion was taught because of the disagreement in the literature in regard to whether the flow of bile into the duodenum was controlled entirely by duodenal tone and motility or by a special sphincter Recent work on the dog by Lueth (72) in our laboratory shows that to explain the observed facts a correlation of both views is necessary His graphic records show that "the vagi exercise a tonic motor control over the musculature surrounding the intramural portion of the common bile duct, which may or may not be correlated with changes in tone of the duodenal musculature" This confirms Oddi's original contention When one inserts a small cannula through the common duct to the level of the submucosal layer and then exerts pressure, the ampulla may be seen to bulge and the pressure must be raised to an adequate threshold before fluid flows into the duodenum The sphincter of the papilla exerts a pressure of from 2 to 13 cm of H_2O or from one-third to one-sixth of the total resistance of the intramural portion of the common bile duct Graphic records were obtained showing a decreased intramural resistance with duodenal relaxation, which confirm the observations of Elman and McMaster (49), Copher and Kodama (73), Burget (69) and others (74) Apparently then the intramural portion of the common bile duct possesses a special sphinc-

teric mechanism which is intimately coordinated with duodenal peristalsis but which may function independently This interpretation of the facts agrees with the observation of Giordano and Mann (74) who report that bile may spurt from the papillary orifice without discernible peristalsis, but if peristaltic waves are present in the duodenum, the outflow will occur with the peristalses (74a)

Even though duodenal and sphincteric activity may be evident while the gall bladder is evacuating, it does not follow that the activity of these parts is the cause of the evacuation Berg and Jobling (77) have divided the common duct and implanted it into another portion of the duodenum and obtained filling and evacuation of the gall bladder As pointed out above, considerable peristaltic activity of the duodenum of man and dog (Higgins has observed the same in the fish) may occur without evacuation of the gall bladder When the sphincteric resistance in the dog is abolished by section (25) (51), or by a large glass cannula (74) (75) (76) (40) placed in the intramural portion of the common duct, more or less spontaneous emptying occurs within six to eighteen hours Then almost complete emptying is induced by fat feeding This early spontaneous emptying is to be expected since the pressure in the gall bladder during fasting frequently amounts to from 4 to 8 cm of bile (13) and the resistance offered by the sphincter of the common duct may amount to from 20 to 30 cm of bile According to Whitaker (25), if the gall bladder of the cat is only partly filled with iodized oil and the sphincter cut, no emptying occurs until fat is fed These experiments indicate that with the sphincter abolished, the elastic recoil and tonus of the musculature of the gall bladder expel only a portion of the bile They are not free from objection in that viscous iodized oil was used and in the experiments in which iodized bile has been used, the section of the sphincter may have been followed by edema These objections, however, are fully met by the experiments of Higgins and Mann cited above, in which the hepatic ducts were ligated and the common duct cannulated and no bile flowed from the gall bladder until fat was introduced into the duodenum We must therefore conclude that the common-duct sphincter and duodenal musculature assist gall-bladder evacuation by relaxing and thereby permitting bile to be expelled by the contracting gall bladder, and that the "elastic recoil,"

"the ebb and flow of bile," and sudden changes in intra-abdominal pressure are minor factors

The common-duct sphincter may inhibit gall-bladder evacuation The common-duct sphincter and duodenal tone play an important rôle in inhibiting gall-bladder evacuation via the cystic duct The fact that the intramural portion of the common duct in the dog may exert a resistance of from 0 to 75 cm of bile under various conditions and that the gall bladder exerts only a maximal pressure of from 20 to 30 cm , shows that in the presence of high intramural resistance, the gall bladder may contract without evacuating This accounts for the observation that after fat or cholecystokinin, the hepatic ducts in the cat, dog and man are sometimes visualized Thus, the gall bladder may contract against a contracted sphincter (13) (23) (79) This fact, first suggested by Meltzer, is of considerable pathologic importance, since it has been shown experimentally that chemical duodenitis (80) and duodenal stasis (81) (82) delay the rate of emptying of the gall bladder

It is an interesting fact that the maximal power of the gall bladder to contract is approximately the same as the secretory pressure of bile and that both are greater than the "average" common-duct sphincteric pressure in the "intact" dog

Effect of gastro-intestinal operations on gall-bladder evacuation It is worthy of note that various gastro-intestinal operations, such as gastrectomy (56) (67), gastro-enterostomy (24) (25), pyloroplasty of various types (83) do not affect the response of the gall bladder to a fat meal The same is true if the stomach is anastomosed to the jejunum and the duodenal secretions emptied into the ileum (83), which should be expected to occur on either a hormone or reflex basis

Sphincter at the neck of the gall bladder A possible factor concerned in filling and evacuation of the gall bladder which deserves more attention than it has received is that a sphincter may be located at the junction of the gall bladder and cystic duct Certain observations made by Volborth (84) may be explained on this basis, and Mann (85) (48) has obtained differences in pressure between the gall bladder and cystic duct which are best accounted for by a sphincter at the neck of the gall bladder This report deserves further careful investigation (The author omits intentionally a discussion of the valves of Heister

because the diverse opinions of their functional activity are based primarily on anatomic theory (1) (16) (86))

Gall bladder evacuation in cholecystitis It is important to know from a clinical and physiological view point whether the acutely inflamed gall bladder will evacuate If an acutely inflamed gall bladder does not evacuate, this would indicate that the prime mechanism for evacuation lies within the vesicle Graham (22) has written that "shadows of diseased gall bladders were found by cholecystography, not to change in size when the pathological change in the wall were moderately advanced" Recently Murphy (87) and Murphy and Higgins (88) have found in the dog that the acutely inflamed gall bladder, induced chemically, will not empty iodized oil after a fat meal From four to six weeks later, however, the ability of the gall bladder to contract and evacuate returns They report that lesions were not found outside of the gall bladder Obviously in the acute condition the various extrinsic forces alleged to cause gall-bladder evacuation were operating but failed to produce an effect Hence, according to these observations, the acutely inflamed gall bladder does not empty because its contractile mechanism can not be excited to contract

Does the gall bladder evacuate completely every day? With the evidence at hand, I am convinced that the gall bladder of most normal dogs and cats will evacuate or renew its contents every day on a diet containing adequate fat and protein On the basis of the cholecystographic observations of Boyden, Whitaker and others, the same statement is true for normal human subjects Case (41) states that within three hours following a fat meal (two egg yolks, a glass of cream and milk, half and half), the area of the vesicular shadow should be reduced seven-eighths or more in a normal subject Whether or not the gall bladder will renew its contents daily depends on the nature of the diet, the eating habits, and the individual variation I suspect that if a large series of "normal" subjects were studied, rather wide physiological variations would be found as is true for the colon

Summary The gall bladder of all animals studied, including man, possesses contractility and evacuates via the cystic duct, especially on the ingestion of fatty foods In the dog a maximal gall-bladder contraction exerts a force of from 20 to 30 cm of bile pressure on its

contents Contraction of the gall bladder is due primarily to hormone stimulation and in part to nervous reflex excitation The hormone is secretin-like chemically and is produced chiefly by the upper intestinal mucosa upon contact with dilute hydrochloric acid, and very probably certain fatty and other substances which cause secretin production, but which have not yet been tested by cross-circulation experiments The intravenous injection of the hormone tentatively called cholecystokinin, causes gall-bladder evacuation in animals, including man *The gall bladder empties primarily by the contraction of its musculature* Other factors, such as the "ebb and flow of bile," "elastic recoil," and "intra-abdominal pressure changes," play a minor rôle The common-duct sphincter and duodenal musculature assist evacuation chiefly by relaxing and thereby permitting bile to pass from the contracting vesicle into the duodenum The fact that an abnormally tonic common-duct sphincter or duodenum may cause sufficient resistance to overpower the contractile force of the gall bladder and the secretory pressure of the liver is, I believe, of considerable pathologic importance

REFERENCES[3]

(1) Sweet Internat Clin, 34 187, 1924, Ann Surg, 90 939, 1929
(2) Halpert Med Klin, 20 408, 1924, Am J Physiol, 88 351, 1929
(3) Demel and Brummelkamp Mitt a d Grenzgeb d Med u Chir, 37 515, 1924
(4) Blond Arch f klin Chir, 149 662, 1928
(5) Galen On the Natural Faculties, Translation by A J Brock, New York, 1916
(6) Haller Elementa Physiologiae, 1764
(7) Doyon Arch d Physiol Norm et Path, 5 678, 711, 1893
(8) Bainbridge and Dale J Physiol, 33 138, 1905
(9) Freese Johns Hopkins Hosp Bull, 16 235, 1905
(10) Okada J Physiol, 50 42, 1915
(11) Taylor and Wilson Am J Physiol, 74 172, 1925
(12) Chiray and Pavel Am J Med Sci, 172 11, 1926
(13) Ivy and Oldberg Am J. Physiol, 86 599, 1928
(14) Lueth, Ivy and Kloster Am J Physiol, 91 329, 1929
(15) Ravdin Arch Surg, 22 810, 1931
(16) Babkin Aussere Sekretion der Verdauungsdrusen, 2nd Edition, Berlin, 1928
(17) Meltzer Am J Med Sci, 153 469, 1917
(18) Lyon J A M A, 73 980, 1919, Arch Int Med, 43 147, 1929
(19) Auster and Crohn Am J Med Sci, 164 345, 1922.
(20) Winkelstein Arch f Verdauungs-Krankheit, 32 7, 1923, Am J Med Sci, 168 812, 1924, Ibid, 169 679, 1925, J A M A, 80 1748, 1923

[3] This bibliography is admittedly incomplete

(21) Mann Physiol Reviews, 4 251, 1924
(22) Graham and Cole J A M A, 82 613, 1924, Graham et al, Diseases of the Gall Bladder and Bile Ducts, Philadelphia, 1928
(23) Boyden Anat. Rec, 30 333, 1925, Ibid, 33 201, 1926
(24) Sosman, Whitaker and Edson Am J Roent Rad Therap, 14 495, 1925
(25) Whitaker Am J Physiol, 78 411, 1926
(26) McMaster and Elman J Exper Med, 44 173, 1926
(27) Higgins and Mann Am J Physiol, 78 339, 1926
(28) Burget and Brocklehurst Am J Physiol, 83 578, 1927–1928
(29) Ivy, Sacks and Drewyer Moving Picture Film (may be borrowed on application to A C Ivy)
(30) Halpert and Hanke Am J Physiol, 88 351, 1929
(31) Rewbridge, Hanke and Halpert Am J Physiol, 95 511, 1930
(32) Walsh and Ivy Am J Physiol 100 594, 1932
(33) Higgins Arch Surg, 16 1021, 1928
(33a) Babkin and Webster Canad Med Asso Journ, 21 32, 1929
(34) Sachs Nebraska Med J, 6 225, 1921
(35) Pribram Klin Wochenschr, 2 1590, 1923
(36) Matsuo J A M A, 83 1289, 1924
(37) Trommer and Hempel Klin Wochenschr, 6 678, 1927
(38) Lake Am J Med Sci, 174 786, 1927
(39) Johnson J Clin Invest, 10 9, 1931
(39a) Delario J Lab Clin Med, 16 329, 1930–1931
(40) Crandall Arch Int Med, 48 1217, 1931
(41) Case J A M A, 92 291, 1929
(42) Adlersberg and Taubenhaus Biochem Zeitschr, 177 400 1926
(43) Jones and Walsh Am J Physiol 101 1, 1932
(44) Boyden Surg, Gynec and Obstet., 46 30, 1928
(45) Ivy, Drewyer and Orndoff Endocrinology, 14 343, 1930
(46) Pendergrass Loc cit, Ravein, Reference 15
(47) Boyden and Birch Am J Physiol, 92 287, 301, 1930
(48) Potter and Mann Am J Med Sci, 171 202, 1926
(49) Elman and McMaster J Exper Med, 44 151, 1926
(50) Carlson and Litt Arch Int Med, 33 281, 1924
(51) Boyden and Birch Proc Soc Exper Biol and Med, 24 827, 1927
(52) Boyden Proc Soc Exper Biol and Med, 25 99, 1927
(53) Krause and Whitaker Am J Physiol, 87 172, 1928
(54) Ivy Physiol Reviews, 10 282, 1930, Also unpublished work
(55) Copher and Illingworth Surg, Gynec and Obstet, 46 459 1928
(56) Whitaker Arch Surg, 18 1785, 1929
(57) Higgins and Wilhelmj Am J Med Sci, 178 805, 1929
(58) Silverman and Dennis Radiology, 11 45, 1928
(59) Bassin and Whitaker New England Med J, 202 311, 1930
(60) Ivy, Kloster, Lueth and Drewyer Am J Physiol, 91 336, 1929
(61) Halpert and Lewis Am J Physiol, 93 506, 1930
(62) Ischiyama Mitt a d med Fak d k Univ Kyushu Fukuoka, 10 61, 1925
(63) Mellanby Lancet, 211 215, 1926
(64) Braga and Campos Physiol Abst, 4 329, 1919–1920

(65) Brugsch and Horsters Arch Exp Path u Pharm, 118 267, 1926
(66) Jung In press
(67) Morgan, Crandall and Ivy Proc Soc Exper Biol and Med, 29 227, 228, 1931
(68) Drewyer and Ivy Proc Soc Exper Biol and Med, 27 186, 1929
(69) Burget Am J Physiol, 81 422, 1927, Ibid 74 583, 1925, 79 130, 1926
(70) Cannon Mechanical Factors of Digestion, New York, 1911
(71) Kelling Z Biol, 44 161, 1903
(72) Lueth Am J Physiol, 99 237, 1931
(73) Copher and Kodama Arch Int Med, 38 647, 1926
(74) Giordano and Mann Arch Path Lab Med, 4 943, 1927
(74a) Puestow Proc Mayo Clinic, 6 22, 1931
(75) Hamrick Am J Med Sci, 174 168, 1927
(76) Emmerson and Whitaker Am J Physiol, 83 484, 1928
(77) Berg and Jobling Proc Soc Exper Biol and Med, 24 434, 1927
(78) Scott and Whitaker Proc Soc Exper Biol and Med, 25 420, 1927–1928
(79) Scott and Whitaker J A M A, 91 9, 1928
(80) Crain and Walsh Surg, Gynec and Obstet, 53 753, 1931
(81) Walsh Unpublished
(82) Shapiro Unpublished
(83) Pope Am J Med Sci, 78 48, 1929
(84) Volborth J Russe d Physiol, 1 63, 1917–1918
(85) Mann J A M A, 83 829, 1924
(86) Mentzer Arch Surg, 13 511, 1926
(87) Murphy Arch Surg, 21 300, 1930
(88) Murphy and Higgins Arch Surg, 20 756, 1930
(89) Newcomer, Newcomer and Conyers Radiology, 17 317, 1931

MEDICINE

All correspondence relating to the publication of papers should be addressed to the Associate Editor, Doctor Alan Chesney, The Johns Hopkins Hospital, Baltimore, Maryland

Twenty-five reprints, without covers, of articles will be furnished to contributors free of cost Additional reprints, not to exceed 175, may be purchased The Editors and Publishers feel that a large distribution of reprints would interfere with the distribution of MEDICINE When there is a special demand for a particular article, the Publishers endeavor to make such an article available in the series of books known as MEDICINE MONOGRAPHS

Correspondence concerning business matters should be sent to The Williams & Wilkins Company, Publishers of Scientific Books and Periodicals, Mt Royal and Guilford Avenues, Baltimore, Maryland, U S A

The periodical is issued quarterly A volume consists of 500 pages (4 issues of about 125 pages to the issue)

Subscription price Current Volume $5 00, United States and countries within the postal union, $5 50 countries outside the postal union Single copies will be supplied, when available, at the rate of $1 50 a copy

Claims for copies lost in the mails must be made within 30 days (domestic subscribers), 90 days (foreign subscribers) of the date of issue

Changes of address must be received at least two weeks prior to the date of issue

New subscriptions and renewals are entered to begin with the first issue of the current volume Should any issue of the current volume be out of print at the time the subscription order is received, the pro-rata value of such numbers will be credited to the next volume, and the renewal invoice therefore adjusted accordingly

Subscriptions should be renewed promptly—To avoid a break in your series, subscriptions should be renewed promptly The publishers cannot guarantee to supply back issues on belated renewals

Subscriptions, new or renewal, should be sent to the Publishers or to Agents listed below

AGENTS

For Argentina and Uruguay Beutelspacher y Cia, Sarmiento 815 Buenos Aires

For Australia Angus & Robertson, Limited, 89–95 Castlereagh Street, Sydney

For Belgium Henri Lamertin, 58 Rue Coudenberg, Bruxelles.

For the British Empire, except Australia and Canada Bailhère, Tindall & Cox, 8 Henrietta St, Covent Garden, WC 2, London, England

For Canada Wm Dawson & Sons, Ltd, 91 Queen Street East, Toronto

For China Commercial Press Ltd, Paoshan Road, Shanghai, China.

For Denmark H. Hagerup's Boghandel, Gothersgade 30, Kjöbenhavn

For France Emile Bougault, 48 Rue des Ecoles, Paris.

For Germany B Westermann Co, Inc., Zimmerstrasse 35–41 Berlin SW 68, Germany

For Holland Scheltema & Holkema, Rokin 74–76, Amsterdam

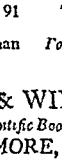
For Japan and Korea Maruzen Company, Ltd (Maruzen Kabushiki Kaisha), 6 Nihonbashi Ton Nichome, Tokyo, Fukuoka, Osaka, Kyoto, and Sendai, Japan

For Spain Ruiz Hermanos, Plaza de Santa Ana, 13, Madrid.

THE WILLIAMS & WILKINS COMPANY

Publishers of Scientific Books and Periodicals

BALTIMORE, U S A



PUBLISHERS OF *Medicine Journal of Urology Journal of Pharmacology and Experimental Therapeutics, American Journal of Tropical Medicine Journal of Immunology Journal of Industrial Hygiene Quarterly Review of Biology Journal of Bacteriology Annals of the Public Thompson Research Laboratory Journal of Biological Chemistry Chemical Reviews Soil Science Social Forces Personnel Journal Journal of Comparative Psychology Mental Measurement Monographs Studies in Psychology and Psychiatry Occupational Therapy and Rehabilitation Child Development Journal of Aviation Medicine The American Journal of Clinical Pathology*